RESULTS OF APPROXIMATION AND MEASURE ON MUTATIONAL SPACES

by

Onyeka E. Obi

BS, University of Pittsburgh, 2004

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This dissertation was presented

by

Onyeka E. Obi

It was defended on

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and approved by

Paul M. Gartside, Department of Mathematics

William J. Layton, Department of Mathematics

Christopher J. Lennard, Department of Mathematics

Robert S. Parker, Department of Chemical and Petroleum Engineering

Dissertation Director: Paul M. Gartside, Department of Mathematics

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Onyeka E. Obi, PhD

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This thesis extends the machinery of Mutational Analysis to accommodate numerical methods that are commonly used today, such as the Midpoint Method, Heun Method, and Runge-Kutta Methods. This is done by developing Taylor expansions in Mutational Spaces of Higher Order. Another extension of Mutational Analysis to Stochastic Mutational Analysis is considered. This extension is used to accommodate more realistic and robust models than the deterministic counterpart. A biologically relevant model is used as an illustration of this extension.

TABLE OF CONTENTS

LIST OF FIGURES

1.0   INTRODUCTION

1.1   THE MOTIVATION AND THE PLAN

In medicine, solid tumor growth beyond a certain point requires resources provided by the host's vascular system [23].   One of the many cancer therapies consists of antiangiogenic agents that target the portion of the vascular system supplying tumor growth [16].   It has been shown experimentally that antiangiogenic therapy can sometimes aggravate tumor growth instead of attenuating it.   Biologists have suggested two mechanisms for this paradoxical behavior.   One mechanism requires cancer cells to send out signals that recruit blood vessels to replace those that have been deactivated by medication, by a process called vascular co-option [23].   Another mechanism requires that cancer masses develop their own vessels to reconnect to the surrounding vasculature, by a process called vasculogenic mimicry[23].   These kinds of dynamics are geometrically driven, and may benefit from a flexible gemometric description.   While this interesting problem is the original motivation for the theory to follow, other applications have encouraged work associated with the theory to follow.   For a survey on antiangiogenic medication, see [14].

One example from a different point of view comes from networked surveillance [8].   Historically, surveillance footage of multiple locations are collected and searched for geometric targets, which are then segmented and tracked over recorded time.   Each target is segmented as a separate object and followed independently.   However, it has been suggested that multiple objects can be tracked simultaneously as a single geometric object.   The mathematics used to do this is related to a predecessor of the current work, but not the current work itself.
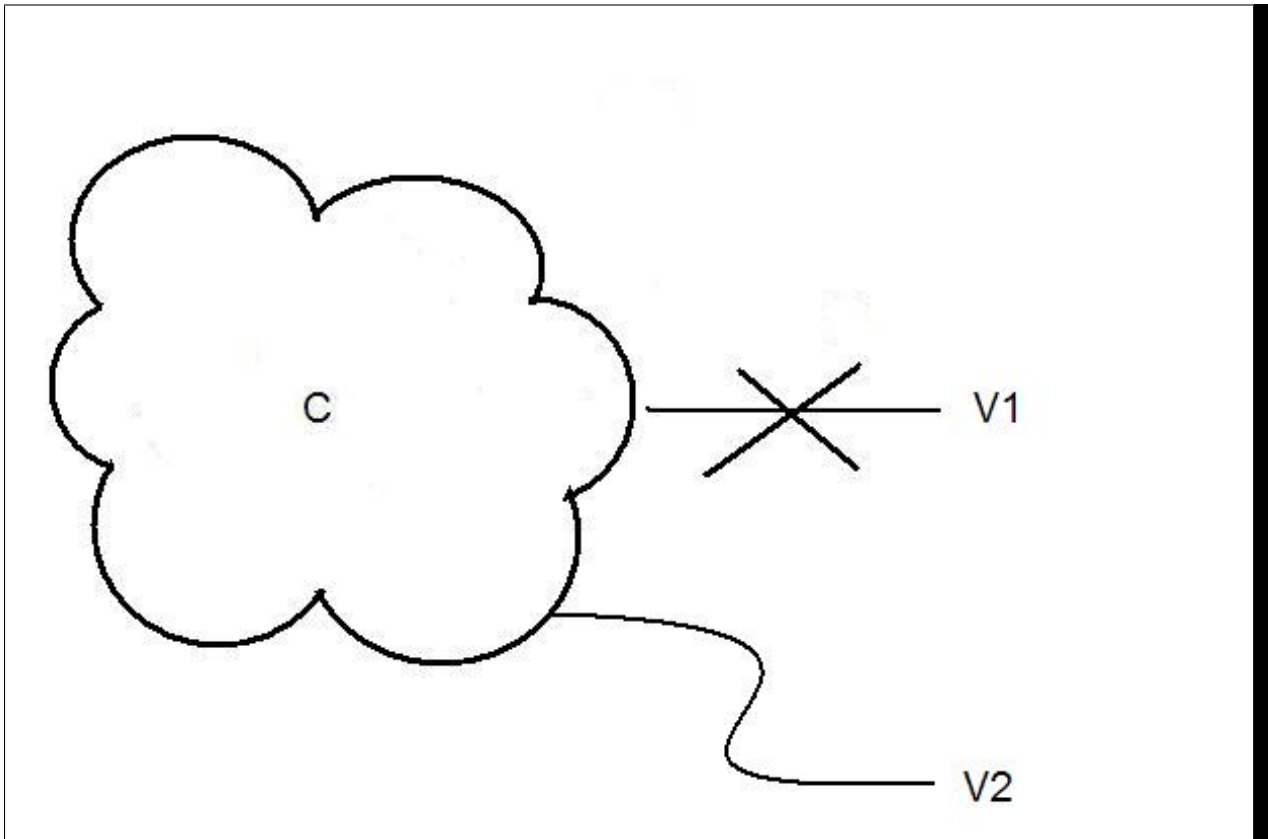
Figure 1.1.1: Vascular Cooption: Blood vessel V1 is deactivated by medication, then the tumor mass C sends signals out, recruiting V2 in the process.
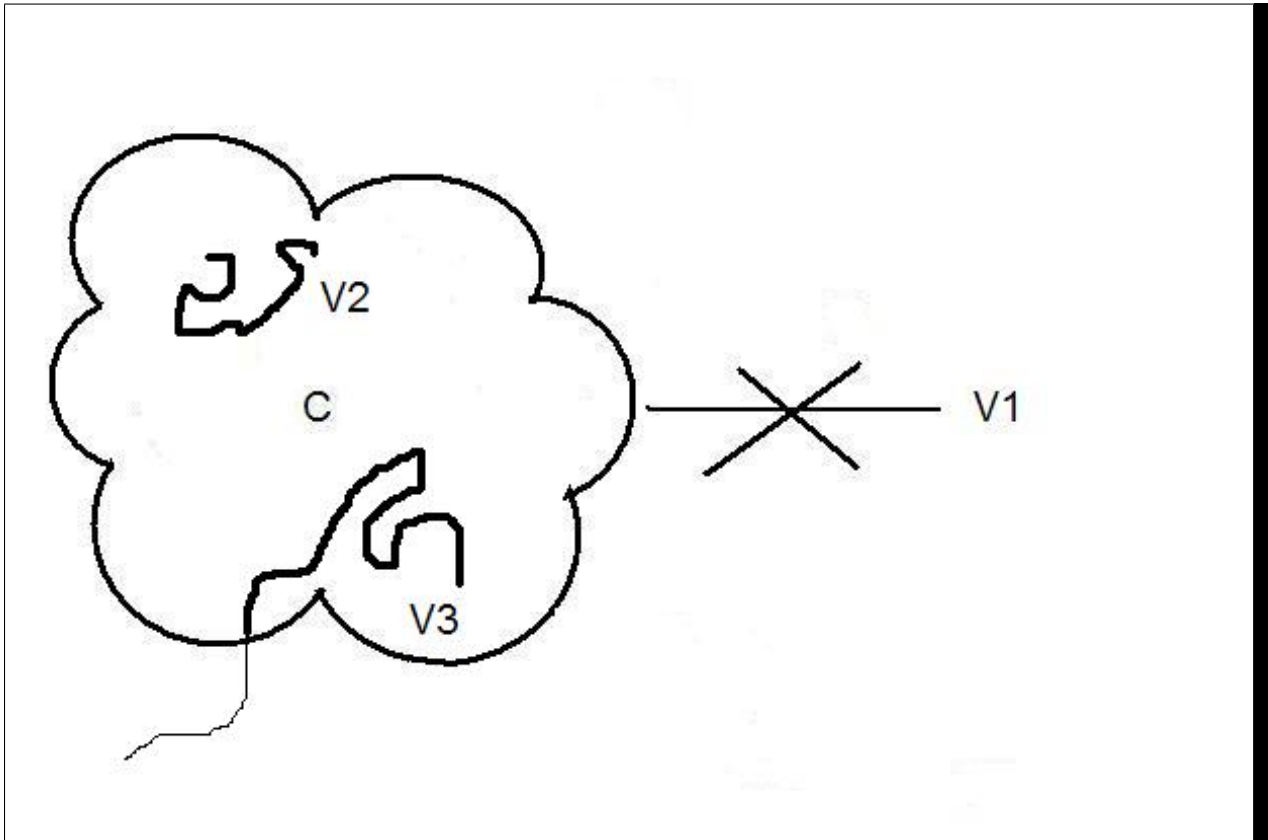
Figure 1.1.2: Vasculogenic Mimicry: V1 is deactivated by medicine, then the tumor mass C develops its own blood vessels V2 and V3 in order to connect to the outside network of vessels.

The modern theory of differential equations on metric spaces began with the work of [25] on quasidifferential equations. Recently, [6] have advanced the theory, motivated by balanced flows in metric spaces. Jean-Pierre Aubin took the theory in another direction in order to study visual control and mathematical morphology. His seminal paper [1] established the theory of mutational equations on metric spaces, which then led to [2], subsequently inspiring the author to pursue the theory in the present work. Generalizations to mutational equations on general topological spaces has been carried out in [18, 19, 20]. The focus, so far, has been on existence results, with [6] briefly mentioning Euler approximations. Until now, approximation of mutational equations outside of the Euler method have not been explored. There also has been, as of yet, no attempt to treat stochastic flows in the general theory. The present work seeks to accomplish both objectives.

The current work is a substantial expansion in mutational analysis. There are several reasons why this expansion is valuable. As a theory of calculus on metric spaces, it computes directly with geometric evolutions, without a need to designate parameters to evolve, such as volume or concentration. As a result, one does not have to know a priori which parameters of a geometric object actually matter in determining its dynamics. Thus, is it not necessary to follow a tumor "volume" or a wave "amplitude". The objects themselves are described non-parametrically. Also, mutational analysis is a proper generalization of ordinary and partial differential equations, in that it makes perfect sense to consider general shape evolutions and particle or field evolutions together. As a theory of calculus on topological spaces, we can take analogies with differential equations to its logical extreme. As topological spaces are ubiquitous in analysis and geometry, one can assert that mutational analysis provides a notion of calculus for nearly all of mathematics. In other words, a study of mutational analysis can be thought of as a study of calculus in the most general form. Since all physical laws can be stated in the language of calculus, one can also say mutational analysis is a study of physics in its most general form.

Before outlining the agenda of the current work, a brief list of topics related to the history of the current topic will be given. First, the term "calculus on metric spaces" has been used in reference to metric spaces $M^{1,p}$ discovered by Piotr Hajłasz in the 1990s. To be crystal clear, his work dealt with creating metric spaces that were normally associated

with weak derivatives without the use of derivatives. This stands in obvious contrast to the current work, which is concerned with developing extensions of derivatives on already existing metric spaces. The so-called Hajłasz-Sobolev spaces ($M^{1,p}$) satisfy an inequality similar to the classical Poincare inequality, of course without depending on the use of weak derivatives. In theory, it is possible to consider a Hajłasz-Sobolev space as a mutational space with mutations that do not satisfy the Poincare inequality when the mutations are considered as weak derivatives. In fact, one can say that this will normally be the case. Therefore, Aubin and Hajłasz may share the term "calculus on metric spaces" in name only. The Hajłasz-Sobolev spaces themselves have seen several generalizations, such as the Orlics-Sobolev spaces [32]. For more information on Hajłasz's work on analysis of metric spaces, see [9, 10, 11, 13].

The current work deals with probability measures on infinite-dimensional spaces. One well-known example of this is the Weiner measure [5], built on the sigma-algebra completion of the cylindrical algebra where finite restrictions of the distance between two continuous random variables have a Gaussian law. Although, using the procedure described in the current work, the Weiner measure can be reproduced on the space of continuous random variables, the process is not the same as that traditionally used, and the method to be discussed extends to more general spaces.

It should be mentioned that the new calculus is valid not only for metric spaces, but for all topological spaces. The reasoning behind this is rather straightforward. Because all topological spaces are quasiuniform spaces [26], and quasiuniform spaces can be generated by the collection of all quasiuniformly lower semicontinuous functions on the space [29], these spaces are, in turn, generated by a family of Ostensible metrics, as Lorenz calls them. As a result, much of the theory follows similarly, with some technical considerations, as in [18]. For more background on results linking topological spaces to generalized metrization, see [30, 31, 17, 15].

The discussion will proceed as follows. A background on mutational analysis will be given first. One can consider this a general theory of calculus on spaces of sets with an underlying metric. Second, the notion of second and higher order transitions will be given. These are used to construct the 'derivatives' of set-valued maps. An exposition of

the basics will lead up to Taylor approximation results on metric spaces. An immediate application of these approximations will be the development of various numerical methods (e.g. the Midpoint Method, Runge-Kutta methods). In the second half, we turn to the problem of constructing probability measures on mutational spaces. We do this in order to extend Aubin's framework into a stochastic setting. Once we have done this, we can talk of stochastic mutational equations and their solutions. As an application of this new theory, we will take a look at two spatial models of tumor growth, one deterministic, and one stochastic, in order to compare and highlight the achievements of realism in the stochastic model. The appendix will contain code used to implement the deterministic model.

Before diving into the discussion, one disclaimer should be added. There are many applications of Mutational Analysis, and an exhaustive list of such applications would sum to an entire body of work on its own. There are also many applications of the enhancements to Mutational Analysis made in the current work. However, with the possible exception of the final section, and to maintain brevity and logical coherence throughout, we will restrain ourselves to the mention of applications that best illustrate the new technology that is the primary subject of the current discussion.

1.2   PRELIMINARIES

In this section, we review some facts from Mutational Analysis needed throughout. All of this can be found in [1, 2].

Definition 1. *Let E be a metric space for a distance d. We denote by $\overline{\Theta}(E)$ the space of all maps $\vartheta : [0, T] \times E \to E$ that satisfy*

$$\begin{cases} i) & \vartheta\left(0, x\right) = x \\ \\ ii) & \forall t \in \left[0, T\right], \quad \lim_{h \to 0+} \frac{d(\vartheta(t+h,x),\vartheta(h,\vartheta(t,x)))}{h} = 0 \\ \\ iii) & \alpha\left(\vartheta\right) := \max\left(\sup_{x \neq y}\left(\limsup_{h \to 0+} \frac{d(\vartheta(h,x),\vartheta(h,y))-d(x,y)}{hd(x,y)}\right), 0\right) < +\infty \\ \\ iv) & \beta\left(\vartheta\right) := \sup_{z \in E}\left(\limsup_{h \to 0+} \frac{d(\vartheta(h,z),z)}{h}\right) < +\infty \end{cases}$$

Definition 2. *These maps are called transitions on E.*

Definition 3. *The neutral transition $\mathbb{O}$ is the transition such that $\mathbb{O}\left(h, x\right) = x \; \forall \; h \in \left[0, 1\right]$ and $x \in E$ for a metric space E.*

Definition 4. *A mutational space is a pair $\left(E, \Theta\left(E\right)\right)$ of a metric space and $\Theta\left(E\right)$ a space of transitions, including the neutral transition, that is closed in $\mathcal{C}\left(\left[0, 1\right] \times E, E\right)$ with the distance $d_{\Lambda}\left(\vartheta, \tau\right) := \sup_{z \in E}\left(\limsup_{h \to 0+} \frac{d(\vartheta(h,z),\tau(h,z))}{h}\right)$.*

Definition 5. *Consider two mutational spaces $\left(E, \Theta\left(E\right)\right)$, $\left(F, \Theta\left(F\right)\right)$ and a single-valued map $f : E \to F$. We shall say that the mutation $\overset{\circ}{f}\left(x\right)$ of f at x is the set-valued map from $\Theta\left(E\right)$ to $\Theta\left(F\right)$ defined by*

$$\tau \in \overset{\circ}{f}\left(x\right)\vartheta \iff \lim_{h \to 0+} \frac{d\left(f\left(\vartheta\left(h, x\right)\right), \tau\left(h, f\left(x\right)\right)\right)}{h} = 0$$

Definition 6. *We shall say that f is mutable at x in the directions $\vartheta \in \Theta\left(E\right)$ if $\overset{\circ}{f}\left(x\right)\vartheta$ is nonempty for every $\vartheta \in \Theta\left(E\right)$.*

Definition 7. *For $\left(E, \Theta\left(E\right)\right)$ a mutational space, $a \in \mathbb{R}^{+}$, $x \in E$, and $\theta \in \Theta\left(E\right)$, $\theta\left(a, x\right) = a\theta\left(1, x\right)$.*

We need this definition in order to clarify that transitions are supposed to behave like they do in the classical sense. For example, if we start at a position $x \in \mathbb{R}^n$, we can move in a direction $v \in \mathbb{R}^n$ by evaluating $x + v$. We can also scale v by an $a \in \mathbb{R} \backslash \{0\}$ and move from x to $x + av$.

Notation 8. *We will often write $a \cdot \theta + x$ to stand for $a\theta(1, x)$.*

We will use the following facts repeatedly:

Lemma 9 (T). *Consider two transitions ϑ and τ. Then, for all $h \in [0, 1)$,*

$$d(h \cdot \vartheta + x, h \cdot \tau + y) \leq d(x, y) e^{\alpha(\vartheta)h} + hd_\Lambda(\vartheta, \tau) \frac{e^{\alpha(\vartheta)h} - 1}{\alpha(\vartheta) h}$$

Consequently, we infer that

$$\frac{d(h \cdot \vartheta + x, h \cdot \tau + y) - d(x, y)}{h} \leq \frac{e^{\alpha(\vartheta)h} - 1}{h} d(x, y)$$

and that

$$\begin{cases} i) & \|\vartheta(x)\| := \sup_{h \in [0,1[} \frac{d(h \cdot \vartheta + x, x)}{h} \leq \beta(\vartheta) \frac{e^{\alpha(\vartheta)} - 1}{\alpha(\vartheta)} \\ \\ ii) & \|\vartheta\|_\Lambda := \sup_{h \in [0,1[,\; x \neq y} \frac{d(h \cdot \vartheta + x, \vartheta(h,y))}{d(x,y)} \leq e^{\alpha(\vartheta)} \end{cases}$$

Lemma 10 (M). *Let $(E, \Theta(E))$ be a mutational space. Consider two measurable functions*

$t \to \vartheta(t)$ *and* $t \to \tau(t)$ *from an interval $[0, T] \subset \mathbb{R}$ to $\Theta(E)$ supplied with the distance d_Λ and their primitives $x(\cdot)$ and $y(\cdot)$ starting at x_0 and y_0, respectively. Assume that*

$$\mu(t) := \int_0^t \alpha(\vartheta(s)) \, ds < +\infty$$

Then

$$d(x(t), y(t)) \leq d(x_0, y_0) e^{\mu(t)} + \int_0^t e^{\mu(t) - \mu(s)} d_\Lambda(\vartheta(s), \tau(s)) \, ds$$

8

In particular, from any initial state x_0 starts a unique primitive of $t \mapsto \vartheta(t) \in \Theta(E)$ satisfying

$$\frac{d\left(x\left(t+h\right), h \cdot \vartheta\left(t\right) + x\left(t\right)\right)}{h} \leq \frac{1}{h} \int_0^h e^{\mu(t)-\mu(s)} d_\Lambda\left(\vartheta\left(t+s\right), \vartheta\left(t\right)\right) ds$$

and that

$$\forall\, t, s \in [0, T]\,, \ d\left(x\left(t\right), x\left(s\right)\right) \leq c \frac{e^{MT} - 1}{M} \left|t - s\right|$$

whenever $\vartheta\left(\cdot\right)$ is skirted and bounded in the sense that

$$M := \sup_{t \in [0,T]} \alpha\left(\vartheta\left(t\right)\right) < +\infty\ \ \&\ \ c := \sup_{t \in [0,T]} \beta\left(\vartheta\left(t\right)\right) < +\infty$$

Theorem 11 (Cauchy-Lipschitz)**.** *Let X be a finite dimensional vector space. Let $f : X \to X$ be a Lipschitz map with Lipschitz constant $\|f\|_\Lambda$. Fix a differentiable function $y\left(\cdot\right) : [0, T] \to X$. Then there exists a unique solution $x\left(\cdot\right)$ to the Cauchy problem for the differential equation $x' = f\left(x\right)$ satisfying the inequality*

$$\begin{cases} \forall\, t \in [0, T]\,, \ d\left(x\left(t\right), y\left(t\right)\right) \leq \\[2ex] e^{\left(M + \|f\|_\Lambda\right)t} d\left(x_0, y\left(0\right)\right) + \int_0^t e^{\|f\|_\Lambda(t-s)} \left\|f\left(y\left(s\right)\right) - y'\left(s\right)\right\| ds \end{cases}$$

Theorem 12 (Filippov)**.** *Assume that $F : X \rightsquigarrow X$ is $\lambda - Lipschitz$ with nonempty closed values on the interior of its domain. Let $y\left(\cdot\right)$ be a given absolutely continuous function such that $t \to d\left(y'\left(t\right), F\left(y\left(t\right)\right)\right)$ is integrable $\left(\text{for the measure } e^{-\lambda s} ds\right)$. Then there exists a solution $x\left(\cdot\right)$ to the differential inclusion*

$$\text{for almost all } t \in [0, T]\,, \quad x'\left(t\right) \in F\left(x\left(t\right)\right)$$

such that, for all $t \geq 0$,

$$\left\|x\left(t\right) - y\left(t\right)\right\| \leq e^{\lambda t}\left(\left\|x_0 - y\left(0\right)\right\| + \int_0^t d\left(y'\left(s\right), F\left(y\left(s\right)\right)\right) e^{-\lambda s} ds\right)$$

and for almost all $t \in [0, T[$,

$$\begin{cases} \left\|x'\left(t\right) - y'\left(t\right)\right\| \leq d\left(y'\left(t\right), F\left(y\left(t\right)\right)\right) \\[2ex] + \lambda e^{\lambda t}\left(\left\|x_0 - y\left(0\right)\right\| + \int_0^t d\left(y'\left(s\right), F\left(y\left(s\right)\right)\right) e^{-\lambda s} ds\right) \end{cases}$$

9

Remark 13. *Filippov uses $\rightsquigarrow$ to indicate a set-valued mapping. On the other hand, we will use the more standard notation $F : X \to 2^X$.*

Remark 14. *$\lambda - Lipschitz$ simply means Lipschitz mapping with Lipschitz constant λ. For $x_1, x_2 \in E$ a metric space, this means that $\mathbb{D}\left(F\left(x_1\right), F\left(x_2\right)\right) \le \lambda d\left(x_1, x_2\right)$, where $\mathbb{D}$ is the Hausdorff distance.*

We now illustrate some examples of first-order transitions.

Example 15. *Let $x, v \in \mathbb{R}^n$. The classical transition derived from v is the map $\vartheta_v\left(h, x\right) = x + hv$, for $h > 0$. This makes $\left(\mathbb{R}^n, \mathbb{R}^n\right)$ into a mutational space.*

Example 16. *Let $B \in \mathcal{KC}\left(\mathbb{R}^n\right)$. The structuring transition derived from B is the map $\vartheta_B\left(h, x\right) := x + hB$. Adding the neutral transition, $\left(\mathcal{K}\left(\mathbb{R}^n\right), \mathcal{KC}\left(\mathbb{R}^n\right)\right)$ becomes a mutational space.*

Example 17. *Let $\varphi \in Lip\left(\mathbb{R}^n, \mathbb{R}^n\right)$. Define the map $\vartheta_\varphi\left(h, x\right) = x\left(h\right)$, where $x\left(h\right)$ is the solution to the differential equation $x'\left(t\right) = \varphi\left(x\left(t\right)\right)$ starting at x. Now, for $K \in \mathcal{K}\left(\mathbb{R}^n\right)$, define $\vartheta_\varphi\left(h, K\right) = \left\{x\left(h\right)\right\}_{x \in K}$. Then ϑ_φ is the shape transition derived from φ. It turns $\left(\mathcal{K}\left(\mathbb{R}^n\right), Lip\left(\mathbb{R}^n, \mathbb{R}^n\right)\right)$ into a mutational space.*

Example 18. *Let $\Phi \in LIP\left(\mathbb{R}^n, \mathbb{R}^n\right)$. Define the map $\vartheta_\Phi\left(h, x\right) = x\left(h\right)$, where $x\left(h\right)$ is the solution to the differential inclusion $x'\left(t\right) \in \Phi\left(x\left(t\right)\right)$ starting at x. Now, for $K \in \mathcal{K}\left(\mathbb{R}^n\right)$, define $\vartheta_\Phi\left(h, K\right) = \left\{x\left(h\right)\right\}_{x \in K}$. Then ϑ_Φ is the morphological transition derived from Φ. It turns $\left(\mathcal{K}\left(\mathbb{R}^n\right), LIP\left(\mathbb{R}^n, \mathbb{R}^n\right)\right)$ into a mutational space.*

We have a way to make new mutational spaces from old ones, using finite products.

Theorem 19. *Let $\left(E, \Theta\left(E\right)\right)$ and $\left(F, \Theta\left(F\right)\right)$ be mutational spaces with metrics d_1 and d_2, respectively. Define $\left(E \times F, \overline{\Theta}\left(E \times F\right)\right)$ as follows: For $\theta_1 \in \overline{\Theta}\left(E\right)$, $\theta_2 \in \overline{\Theta}\left(F\right)$, define $\theta \in \overline{\Theta}\left(E \times F\right)$ by $h\theta + \left(x, y\right) = \left(h\theta_1 + x, h\theta_2 + y\right)$, for $\left(x, y\right) \in \left(E, F\right)$. Let the metric for $\left(E \times F, \overline{\Theta}\left(E \times F\right)\right)$ be $d\left(\left(p_1, q_1\right), \left(p_2, q_2\right)\right) = d_1\left(p_1, p_2\right) + d_2\left(q_1, q_2\right)$, for $p_1, p_2 \in E$ and $q_1, q_2 \in F$. Then $\left(E \times F, \overline{\Theta}\left(E \times F\right)\right)$ is a mutational space.*

Proof. 1. $0 \cdot \theta + (x, y) = (0 \cdot \theta_1 + x, 0 \cdot \theta_2 + y) = (x, y)$

2. Fix a $t \in [0, 1[$.

$$
\begin{cases}
\lim\limits_{h \to 0^+} \dfrac{d((t+h)\theta + (x,y), h\theta + t\theta + (x,y))}{h} \\[3em]
= \lim\limits_{h \to 0^+} \dfrac{d(((t+h)\theta_1 + x, (t+h)\theta_2 + y), (h\theta_1 + t\theta_1 + x, h\theta_2 + t\theta_2 + y))}{h} \\[3em]
= \lim\limits_{h \to 0^+} \dfrac{d_1((t+h)\theta_1 + x, h\theta_1 + t\theta_1 + x) + d_2((t+h)\theta_2 + y, h\theta_2 + t\theta_2 + y)}{h} = 0
\end{cases}
$$

3.

$$
\begin{cases}
\max\left(\sup\limits_{x \neq y}\left(\limsup\limits_{h \to 0^+} \dfrac{d(h\theta + (u,v), h\theta + (x,y)) - d((u,v),(x,y))}{h}\right), 0\right) \\[3em]
= \max\left(\sup\limits_{x \neq y}\left(\limsup\limits_{h \to 0^+} \dfrac{d((h\theta_1 + u, h\theta_2 + v), (h\theta_1 + x, h\theta_2 + y)) - d((u,v),(x,y))}{h}\right), 0\right) \\[3em]
= \max\left(\sup\limits_{x \neq y}\left(\limsup\limits_{h \to 0^+} \dfrac{d_1(h\theta_1 + u, h\theta_1 + x) + d_2(h\theta_2 + v, h\theta_2 + y) - d_1(u,x) - d_2(v,y)}{h}\right), 0\right) \\[3em]
= \max\left(\sup\limits_{x \neq y}\left(\limsup\limits_{h \to 0^+} \dfrac{d_1(h\theta_1 + u, h\theta_1 + x) - d_1(u,x) + d_2(h\theta_2 + v, h\theta_2 + y) - d_2(v,y)}{h}\right), 0\right) \\[3em]
\leq \max\left(\sup\limits_{x \neq y}\left(\limsup\limits_{h \to 0^+} \dfrac{d_1(h\theta_1 + u, h\theta_1 + x) - d_1(u,x)}{h}\right), 0\right) \\[3em]
+ \max\left(\sup\limits_{x \neq y}\left(\limsup\limits_{h \to 0^+} \dfrac{d_2(h\theta_2 + v, h\theta_2 + y) - d_2(v,y)}{h}\right), 0\right) < +\infty
\end{cases}
$$

11

4.

$$
\begin{cases}
\sup\limits_{(y,z)\in E\times F}\left(\limsup\limits_{h\to 0^+}\frac{d(h\theta+(y,z),(y,z))}{h}\right) \\[2em]
= \sup\limits_{(y,z)\in E\times F}\left(\limsup\limits_{h\to 0^+}\frac{d((h\theta_1+y,h\theta_2+z),(y,z))}{h}\right) \\[2em]
= \sup\limits_{(y,z)\in E\times F}\left(\limsup\limits_{h\to 0^+}\frac{d_1(h\theta_1+y,y)+d_2(h\theta_2+z,z)}{h}\right) \\[2em]
\leq \sup\limits_{(y,z)\in E\times F}\left(\limsup\limits_{h\to 0^+}\frac{d_1(h\theta_1+y,y)}{h}\right) + \sup\limits_{(y,z)\in E\times F}\left(\limsup\limits_{h\to 0^+}\frac{d_2(h\theta_2+z,z)}{h}\right) < +\infty
\end{cases}
$$

$\square$

It is not necessary that $d = d_1 + d_2$. There are other metrics derived from d_1 and d_2 that will also work.

Corollary 20. $\left(E\times F, \overline{\Theta}\left(E\times F\right)\right)$ *above with the metric* $d = (d_1^n + d_2^n)^{\frac{1}{n}}$, *for* $n \in [1,\infty)$, *is a mutational space.*

Proof. This follows directly from the Minkowski Inequality (see [7]). $\square$

Corollary 21. $\left(E\times F, \overline{\Theta}\left(E\times F\right)\right)$ *above with the metric* $d = \max\{d_1, d_2\}$ *is a mutational space*

Proof. This follows from the fact that either $d = d_1$ or $d = d_2$ on their respective projections.

$\square$

Now we discuss some new results pertaining to Mutational Analysis proper.

Theorem 22 (Taylor-1). *Let* $(E, \Theta(E))$ *be a mutational space,* $x : [0, T] \to E$ *be mutable, and* $\overset{\circ}{x}(t)$ *be Lipschitz with constant* λ. *Then there exists a constant* C *such that for all* $t \geq 0$

$$
d\left(x(t), t\overset{\circ}{x}(0) + x(0)\right) \leq Ct^2
$$

12

Proof. Let $y(t) = t\overset{\circ}{x}(0) + x(0)$. Then y is mutable, $\overset{\circ}{y}(t) = \overset{\circ}{x}(0)$ and $y(0) = x(0)$. By (10),

$$\begin{cases} d(x(t), y(t)) \leq \underset{x(0)=y(0)}{0} + \int_0^t e^{M(t-s)} d_\Lambda \left(\overset{\circ}{x}(s), \overset{\circ}{x}(0) \right) ds \\[3mm] \leq \int_0^t e^{M(t-s)} \lambda s \; ds \\[3mm] \leq Ct^2 \end{cases}$$

$\square$

13

2.0   TRANSITIONS OF HIGHER ORDER

We now give a definition and some examples of second-order transitions on mutational spaces.

Definition 23. *Let (E, d) be a metric space, and $(E, \Theta(E))$ be the corresponding mutational space. A **second mutational space** is a space $(\Theta(E), \Theta(\Theta(E)))$, where the underlying metric space is a space of transitions $(\Theta(E), d)$. The set $(\Theta(\Theta(E)))$ is called a set of **second transitions**. A mutation defined between two second mutational spaces is called a **second mutation**. All of these structures follow the rules of their first-order equivalents.*

Definition 24. *For θ_1 and θ_2 elements of an nth order mutational space, and x an element of an (n-1)th order mutational space, $\theta_2 + \theta_1 + x := \theta_2(1, \theta_1(1, x))$.*

Definition 25. *For θ_1 an element of an nth order mutational space, and θ_2 an element of an (n+1)th order mutational space, $\theta_2 + \theta_1 := \theta_2(1, \theta_1)$.*

2.1   EXAMPLES OF SECOND TRANSITIONS

Theorem 1. *Let E be a space of structuring transitions with the metric d determined by $d(\vartheta_B, \vartheta_C) = \mathbb{D}(B, C)$, where $\mathbb{D}$ is the Hausdorff metric, and $\vartheta_B, \vartheta_C \in E$. Then (E, E) is a mutational space.*

Proof. Here, we show that structuring transitions can serve as transitions on themselves. Thus, we need to show how these second transitions are defined, and then we check each of the properties of transitions. Let $\vartheta_B, \vartheta_C, \vartheta_D \in E$ and define $h\vartheta_C + \vartheta_B = \vartheta_{B+hC}$.

   i) $0 \cdot \vartheta_C + \vartheta_B = \vartheta_{B+0C} = \vartheta_B$

   ii) $(t+h) \cdot \vartheta_C + \vartheta_B = \vartheta_{B+(t+h)C} = \vartheta_{B+tC+hC} = \vartheta_{(B+tC)+hC} = h \cdot \vartheta_C + t \cdot \vartheta_C + \vartheta_B$

iii)

$$\begin{cases} d\left(h\cdot\vartheta_D+\vartheta_B,h\cdot\vartheta_D+\vartheta_C\right)-d\left(\vartheta_B,\vartheta_C\right)=d\left(\vartheta_{B+hD},\vartheta_{C+hD}\right)-d\left(\vartheta_B,\vartheta_C\right) \\[2em] =\mathbb{D}\left(B+hD,C+hD\right)-\mathbb{D}\left(B,C\right) \\[2em] =\sup_{u\in B,v\in D}\inf_{x\in C,y\in D}\|u-x+h\left(y-v\right)\|-\mathbb{D}\left(B,C\right) \\[2em] \leq\sup_{u\in B}\inf_{x\in C}\|u-x\|+h\sup_{v\in D}\inf_{y\in D}\|y-v\|-\mathbb{D}\left(B,C\right) \\[2em] =\mathbb{D}\left(B,C\right)+h\mathbb{D}\left(D,D\right)-\mathbb{D}\left(B,C\right)=0 \end{cases}$$

this implies that $\alpha\left(\vartheta_D\right)=0$.

iv) $d\left(h\cdot\vartheta_D+\vartheta_B,\vartheta_B\right)=d\left(\vartheta_{B+hD},\vartheta_B\right)=\mathbb{D}\left(B+hD,B\right)=\sup_{u\in B,v\in D}\inf_{x\in B}\|u-x+hv\|\leq$
$\sup_{u\in B}\inf_{x\in B}\|u-x\|+\sup_{v\in D}\|hv\|=\mathbb{D}\left(B,B\right)+h\mathbb{D}\left(D,0\right)=h\|D\|$
implies that $\beta\left(\vartheta_D\right)\leq\|D\|$. $\qquad\qquad\square$

Theorem 2. *Let E be a space of structuring transitions with the Hausdorff metric as above, and let $\Theta\left(E\right)$ be a space of shape transitions that preserve convexity. For $\vartheta_B\in E$ and $\vartheta_\phi\in\Theta\left(E\right)$, define $h\cdot\vartheta_\phi+\vartheta_B=\vartheta_{h\vartheta_\phi+B}$. Then $\left(E,\Theta\left(E\right)\right)$ is a mutational space.*

Proof. i) $0\cdot\vartheta_\phi+\vartheta_B=\vartheta_{0\vartheta_\phi+B}=\vartheta_B$

ii) $\left(t+h\right)\cdot\vartheta_\phi+\vartheta_B=\vartheta_{\left(t+h\right)\vartheta_\phi+B}=\vartheta_{h\vartheta_\phi+t\vartheta_\phi+B}=h\vartheta_\phi+\vartheta_{t\vartheta_\phi+B}=h\vartheta_\phi+t\vartheta_\phi+\vartheta_B$

15

iii) Let $\vartheta_B, \vartheta_C \in E$. Then

$$
\begin{cases}
d\left(h \cdot \vartheta_\phi + \vartheta_B, h\vartheta_\phi + \vartheta_C\right) - d\left(\vartheta_B, \vartheta_C\right) = d\left(\vartheta_{h\vartheta_\phi + B}, \vartheta_{h\vartheta_\phi + C}\right) - d\left(\vartheta_B, \vartheta_C\right) \\[2em]
= \mathbb{D}\left(h \cdot \vartheta_\phi + B, h \cdot \vartheta_\phi + C\right) - d\left(\vartheta_B, \vartheta_C\right) \\[2em]
= \sup_{x \in B} \inf_{y \in C} \|h \cdot \vartheta_\phi + x - (h \cdot \vartheta_\phi + y)\| - d\left(\vartheta_B, \vartheta_C\right) \\[2em]
\leq \sup_{x \in B} \inf_{y \in C} e^{\|\phi\|_\Lambda h} \|x - y\| - d\left(\vartheta_B, \vartheta_C\right) \\[2em]
= \left(e^{\|\phi\|_\Lambda h} - 1\right) d\left(\vartheta_B, \vartheta_C\right)
\end{cases}
$$

where the inequality is given by the Cauchy-Lipschitz Theorem (11). Therefore, $\alpha\left(\vartheta_\phi\right) = 1$.

iv) $d\left(h \cdot \vartheta_\phi + \vartheta_B, \vartheta_B\right) = d\left(\vartheta_{h\vartheta_\phi + B}, \vartheta_B\right) = \mathbb{D}\left(h\vartheta_\phi + B, B\right) = \mathbb{D}\left(h \cdot \vartheta_\phi + B, h \cdot \mathbf{1} + B\right) = \sup_{x \in B} \inf_{y \in B} \|h \cdot \vartheta_\phi + x - (h \cdot \mathbf{1} + y)\|$, and by 11

$$
\sup_{x \in B} \inf_{y \in B} \|h \cdot \vartheta_\phi + x - (h\mathbf{1} + y)\| \leq \sup_{x \in B} \inf_{y \in B} \left(e^{\|\phi\|_\Lambda h} \|x - y\| + h \|\phi\|_\infty \frac{e^{\|\phi\|_\Lambda h} - 1}{\|\phi\|_\Lambda h} \right)
$$

and so $\beta\left(\vartheta_\phi\right) \leq \|\phi\|_\infty$. $\qquad\square$

Theorem 3. *Let E be a space of structuring transitions with the Hausdorff metric, and let $\Theta(E)$ be a space of morphological transitions. For $\vartheta_B \in E$ and $\vartheta_\Phi \in \Theta(E)$, define $h \cdot \vartheta_\Phi + \vartheta_B = \vartheta_{h\vartheta_\Phi + B}$. Then $(E, \Theta(E))$ is a mutational space.*

Proof. By the Filippov Theorem 12, given a solution $y(\cdot)$ to the differential inclusion $y' \in \Psi(y)$ starting at y_0, there is a solution to $x' \in \Phi(x)$ starting at x_0 such that

$$
\begin{cases}
\forall t \in [0, T], \|x(t) - y(t)\| \\[2em]
\leq e^{\|\Phi\|_\Lambda t} \|x_0 - y_0\| + \int_0^t e^{\|\Phi\|_\Lambda (t-s)} \mathbb{D}\left(\Phi(y(s)), \Psi(y(s))\right) ds \\[2em]
\leq e^{\|\Phi\|_\Lambda t} \|x_0 - y_0\| + t \sup_{x \in \mathbb{R}^n} \mathbb{D}\left(\Phi(x), \Psi(x)\right) \frac{e^{\|\Phi\|_\Lambda t} - 1}{\|\Phi\|_\Lambda t}
\end{cases}
$$

16

Thus, for any $y(\cdot)$ a solution to $y' \in \Psi(y)$ from $y \in L$

$$
\left\{
\begin{aligned}
&\mathbb{D}(y(t), t \cdot \vartheta_\Phi + K) = \inf_{z \in \vartheta_\Phi(t,x)} \inf_{x \in K} \|z - y(t)\| \\[2ex]
&\leq \inf_{x \in K} e^{\|\Phi\|_\Lambda t} \|x - y\| + t \sup_{\xi \in \mathbb{R}^n} \mathbb{D}(\Psi(\xi), \Phi(\xi)) \frac{e^{\|\Phi\|_\Lambda t} - 1}{\|\Phi\|_\Lambda t} \\[2ex]
&\leq e^{\|\Phi\|_\Lambda t} \mathbb{D}(y, K) + t \sup_{\xi \in \mathbb{R}^n} \mathbb{D}(\Psi(\xi), \Phi(\xi)) \frac{e^{\|\Phi\|_\Lambda t} - 1}{\|\Phi\|_\Lambda t}
\end{aligned}
\right.
$$

In particular, for $y(t) = t \cdot \vartheta_\Psi + L$, we get

$$
\left\{
\begin{aligned}
&\frac{d\left(\vartheta_{t \vartheta_\Psi + L}, \vartheta_{t \vartheta_\Phi + K}\right) - d(\vartheta_L, \vartheta_K)}{t} \\[2ex]
&= \frac{\mathbb{D}(t \cdot \vartheta_\Psi + L, t \cdot \vartheta_\Phi + K) - \mathbb{D}(L, K)}{t} \\[2ex]
&\leq \frac{e^{\|\Phi\|_\Lambda t} - 1}{\|\Phi\|_\Lambda t} \left(\|\Phi\|_\Lambda \mathbb{D}(L, K) + \sup_{\xi \in \mathbb{R}^n} \mathbb{D}(\Psi(\xi), \Phi(\xi)) \right)
\end{aligned}
\right.
$$

from which it follows that

$$
\left\{
\begin{aligned}
&\limsup_{t \to 0^+} \frac{d\left(\vartheta_{t \vartheta_\Psi + L}, \vartheta_{t \vartheta_\Phi + K}\right) - d(\vartheta_L, \vartheta_K)}{t} \\[2ex]
&\leq \|\Phi\|_\Lambda \mathbb{D}(L, K) + \sup_{\xi \in \mathbb{R}^n} \mathbb{D}(\Psi(\xi), \Phi(\xi))
\end{aligned}
\right.
$$

and so, by taking $\Psi = \Phi$, we get that $\alpha(\vartheta_\Phi) \leq \|\Phi\|_\Lambda$. By taking $L = K$ and $\Psi = \mathbb{O}$, we get that $\beta(\vartheta_\Phi) \leq \|\Phi\|_\infty = \sup_{z \in \mathbb{R}^n} \mathbb{D}(\Phi(z), \mathbb{O})$. Finally, by the fact that morphological transitions satisfy a property to be discussed later (2.2), $(h + t) \cdot \vartheta_\Phi + K = h \cdot \vartheta_\Phi + t \cdot \vartheta_\Phi + K$. $\qquad \square$

Theorem 4. *Let E be a space of shape transitions with the metric d defined by $d(\vartheta_\phi, \vartheta_\psi) = \|\phi - \psi\|_\infty$, where $\vartheta_\phi, \vartheta_\psi \in E$. Define ϑ_ϕ by $h \vartheta_\phi + \vartheta_\psi = \vartheta_{\psi + h\phi}$. Then (E, E) is a mutational space.*

Proof. i) $0 \cdot \vartheta_\phi + \vartheta_\psi = \vartheta_{\psi+0\phi} = \vartheta_\psi$

ii) $(t+h) \cdot \vartheta_\phi + \vartheta_\psi = \vartheta_{\psi+(t+h)\phi} = \vartheta_{(\psi+t\phi)+h\phi} = h \cdot \vartheta_\phi + \vartheta_{\psi+t\phi} = h \cdot \vartheta_\phi + t \cdot \vartheta_\phi + \vartheta_\psi$

iii)

$$
\begin{cases}
d\left(h \cdot \vartheta_\phi + \vartheta_\psi, h \cdot \vartheta_\phi + \vartheta_\rho\right) - d\left(\vartheta_\psi, \vartheta_\rho\right) = d\left(\vartheta_{\psi+h\phi}, \vartheta_{\rho+h\phi}\right) - d\left(\vartheta_\psi, \vartheta_\rho\right) \\[2ex]
\qquad = \|\psi + h\phi - \rho - h\phi\| - \|\psi - \rho\| \\[2ex]
\qquad \leq \|\psi - \rho\| + h\|\phi - \phi\| - \|\psi - \rho\| = 0
\end{cases}
$$

so $\alpha\left(\vartheta_\phi\right) = 0$

iv) $d\left(h \cdot \vartheta_\phi + \vartheta_\psi, \vartheta_\psi\right) = \|\psi + h\phi - \psi\| = h\|\phi\|$, so $\beta\left(\vartheta_\phi\right) = \|\phi\|$ $\square$

Theorem 5. *Let E be a space of morphological transitions with the metric d defined by $d\left(\vartheta_\Psi, \vartheta_\Phi\right) = \sup\limits_{z \in \mathbb{R}^n} \mathbb{D}\left(\Psi(z), \Phi(z)\right)$, where $\vartheta_\Psi, \vartheta_\Phi \in E$. Define ϑ_Φ by $h \cdot \vartheta_\Phi + \vartheta_\Psi = \vartheta_{\Psi+h\Phi}$. Then (E, E) is a mutational space.*

Proof. i) $0 \cdot \vartheta_\Phi + \vartheta_\Psi = \vartheta_{\Psi+0\Phi} = \vartheta_\Psi$

ii) $(t+h) \cdot \vartheta_\Phi + \vartheta_\Psi = \vartheta_{\Psi+(t+h)\Phi} = \vartheta_{(\Psi+t\Phi)+h\Phi} = h \cdot \vartheta_\Phi + \vartheta_{\Psi+t\Phi} = h \cdot \vartheta_\Phi + t \cdot \vartheta_\Phi + \vartheta_\Psi$

iii)

$$
\begin{cases}
d\left(h \cdot \vartheta_\Phi + \vartheta_\Psi, h \cdot \vartheta_\Phi + \vartheta_\Gamma\right) - d\left(\vartheta_\Psi, \vartheta_\Gamma\right) = d\left(\vartheta_{h\Phi+\Psi}, \vartheta_{h\Phi+\Gamma}\right) - d\left(\vartheta_\Psi, \vartheta_\Gamma\right) \\[2ex]
\qquad = \sup\limits_{z \in \mathbb{R}^n} \mathbb{D}\left(h \cdot \Phi(z) + \Psi(z), h \cdot \Phi(z) + \Gamma(z)\right) - d\left(\vartheta_\Psi, \vartheta_\Gamma\right) \\[2ex]
\qquad = \sup\limits_{z \in \mathbb{R}^n} \sup\limits_{y \in \Phi(z), v \in \Psi(z)} \inf\limits_{x \in \Phi(z), u \in \Gamma(z)} \\[2ex]
\qquad \|h(y - x) + u - v\| - d\left(\vartheta_\Psi, \vartheta_\Gamma\right) \\[2ex]
\qquad \leq h \sup\limits_{z \in \mathbb{R}^n} \sup\limits_{y \in \Phi(z)} \inf\limits_{x \in \Phi(z)} \|x - y\|
\end{cases}
$$

18

$$\begin{cases} + \sup_{z \in \mathbb{R}^n} \sup_{v \in \Psi(z)} \inf_{u \in \Gamma(z)} \|u - v\| - d\left(\vartheta_\Psi, \vartheta_\Gamma\right) \\\\ = h \sup_{z \in \mathbb{R}^n} \mathbb{D}\left(\Phi\left(z\right), \Phi\left(z\right)\right) \\\\ + \sup_{z \in \mathbb{R}^n} \mathbb{D}\left(\Gamma\left(z\right), \Psi\left(z\right)\right) - \sup_{z \in \mathbb{R}^n} \mathbb{D}\left(\Gamma\left(z\right), \Psi\left(z\right)\right) \\\\ = h \cdot 0 \end{cases}$$

Hence, $\alpha\left(\vartheta_\Phi\right) = 0$.

iv)

$$\begin{cases} d\left(h\vartheta_\Phi + \vartheta_\Psi, \vartheta_\Psi\right) = d\left(\vartheta_{\Psi+h\Phi}, \vartheta_\Psi\right) = \sup_{z \in \mathbb{R}^n} \mathbb{D}\left(\Psi\left(z\right) + h\Phi\left(z\right), \Psi\left(z\right)\right) \\\\ = \sup_{z \in \mathbb{R}^n} \sup_{y \in \Psi(z), v \in \Phi(z)} \inf_{x \in \Psi(z)} \|y - x - hv\| \\\\ \leq \sup_{z \in \mathbb{R}^n} \sup_{y \in \Psi(z)} \inf_{x \in \Psi(z)} \|y - x\| + h \sup_{z \in \mathbb{R}^n} \sup_{v \in \Phi(z)} \|v\| \end{cases}$$

and so $\beta\left(\vartheta_\Phi\right) = \|\Phi\|_\infty$. $\qquad\qquad\square$

Let $\mathcal{B}\left(\mathbb{R}^n\right)$ for fixed n be the $\sigma-$algebra of Borel subsets of Euclidean space. Let $\left(\mathbb{R}^n, \mathcal{B}\left(\mathbb{R}^n\right), dx\right)$ be the standard Lebesgue measure space. Define a metric on $\mathcal{B}\left(\mathbb{R}^n\right)$ in the following way: Let $B, C \in \mathcal{B}\left(\mathbb{R}^n\right)$. Then $d\left(B, C\right) = \int |1_B - 1_C|\, dx$. Now let us split $\mathcal{B}\left(\mathbb{R}^n\right)$ into equivalence classes by defining $[A] = \{E \in \mathcal{B}\left(\mathbb{R}^n\right) : d\left(A, E\right) = 0\}$. We will assume from here on to deal with equivalence classes, so that whenever we write A, we mean $[A]$. Furthermore, define $[hA] = \left\{E \in \mathcal{B}\left(\mathbb{R}^n\right) : \int_E dx = h \int_A dx\right\}$, and, for $L \in \mathcal{B}\left(\mathbb{R}^n\right)$, $t, h \in \mathbb{R}$, define $[tL \oplus hL] = \{P \cup Q : P \cap Q = \emptyset, P = tL, Q = hL\}$. In the additive notation of transitions from mutational analysis, define a map $\vartheta_F : [0, 1] \times \mathcal{B}\left(\mathbb{R}^n\right) \mapsto \mathcal{B}\left(\mathbb{R}^n\right)$ by $h\vartheta_F + G = G \oplus hF$, for $F, G \in \mathcal{B}\left(\mathbb{R}^n\right)$, with $F \cap G = \emptyset$. We will, perhaps ambiguously, call these Borel structuring transitions.

Theorem 6. $\left(\mathcal{B}\left(\mathbb{R}^n\right), \mathcal{B}\left(\mathbb{R}^n\right)\right)$ *is a mutational space with the transitions* ϑ_F *defined above, for* $F \in \mathcal{B}\left(\mathbb{R}^n\right)$.

Proof. i) $0 \cdot \vartheta_F + G = G \oplus 0 \cdot F = G$

ii) $(t + h) \cdot \vartheta_F + G = h \cdot \vartheta_F + t \cdot \vartheta_F + G$ by definition of $hF \oplus tF$

iii) Let $F, G, H \in \mathcal{B}(\mathbb{R}^n)$.

$$d(h \cdot \vartheta_F + G, h \cdot \vartheta_F + H) - d(G, H) = \int |h \cdot 1_F + 1_G - h \cdot 1_F - 1_H| \, dx - \int |1_G - 1_H| \, dx = 0$$

Therefore, $\alpha(\vartheta_F) = 0$.

iv) $d(h \cdot \vartheta_F + G, G) = \int |h \cdot 1_F + 1_G - 1_G| \, dx = h \int 1_F dx$, so that $\beta(\vartheta_F) = \|F\|_\infty = d(F, \{0\})$ $\qquad \square$

Corollary 7. $(\mathcal{B}(\mathbb{R}^n), \mathcal{B}(\mathbb{R}^n))$ *is a second mutational space with the transitions* ϑ_F, $F, G \in \mathcal{B}(\mathbb{R}^n)$, *defined by* $h \cdot \vartheta_F + \vartheta_G = \vartheta_{h\vartheta_F + G}$.

Remark 8. $(\mathbb{R}^n, \mathbb{R}^n)$ *is also a second mutational space, exactly for the reason it is a first mutational space.*

2.2   THE SECOND ORDER TAYLOR THEOREM FOR MUTATIONAL SPACES

We now list a few axioms of first and second transitions that will aid us in the remainder of the discussion:

Let x be an arbitrary element of an nth order mutational space, θ and θ_1 arbitrary elements of the corresponding (n+1)th-order mutational space, θ_2 an arbitrary element of the corresponding (n+2)th-order mutational space, $\mathbb{O}_1$ the neutral element of the (n+1)th-order mutational space, and t and h positive real numbers.

Axiom S: $t \cdot \theta + h \cdot \theta + x = (t + h) \cdot \theta + x = h \cdot \theta + t \cdot \theta + x$

Axiom A: $t \cdot (h \cdot \theta_2 + \mathbb{O}_1) + x = h \cdot (t \cdot \theta_2 + \mathbb{O}_1) + x$

Axiom B: $t \cdot (h \cdot \theta_2 + \theta_1) + x = t \cdot (h \cdot \theta_2 + \mathbb{O}_1) + t \cdot \theta_1 + x$

Axiom C: For a constant c, whenever $c \cdot \theta_2 + c \cdot \theta_1$ is well-defined, we have

$$c \cdot \theta_2 + c \cdot \theta_1 = c \cdot (\theta_2 + \theta_1)$$

Stylistically, thesis axioms are stated so as to identify the intuition from ordinary calculus. An alternative notation would be the original one of Aubin, but it is more difficult to digest. For example, axiom B would read $\theta_2 (h, \theta_1 (t, x)) = [\theta_2 (h, \mathbb{O}_1)] (t, \theta_1 (t, x))$.

Before we make use of these properties, we now show that they hold for a sufficient number of examples.

Proposition 1. *Let $(E, \Theta (E))$ be a mutational space. For any $\theta \in \Theta$, $x \in E$, and $t, h \in [0, 1]$ with $t + h \leq 1$:*

$$\theta (t, \theta (h, x)) = \theta (t + h, x) \qquad (S)$$

Proof. Fix θ, x, and h. Define $x, y : [0, 1 - h] \mapsto E$ by:

$$x (t) = \theta (t, \theta (h, x)), \quad y (t) = \theta (t + h, x)$$

We check (a) $x (0) = y (0)$, (b) $\theta \in \overset{\circ}{x}$, and (c) $\theta \in \overset{\circ}{y}$. For then, by 11, $x (t) = y (t)$. First, (a) is trivial, since $x (0) = \theta (h, x) = y (0)$. Second, (b) is immediate from the definition of a transition. Third, (c) is also immediate from the definition of a transition, but we verify it for completeness:

$$\begin{cases} \lim\limits_{k \to 0^+} \frac{d(\theta(k,y(t)),y(t+k))}{k} = \lim\limits_{k \to 0^+} \frac{d(\theta(k,\theta(t+h,x)),\theta((t+k)+h,x))}{k} \\ = \lim\limits_{k \to 0^+} \frac{d(\theta(k,\theta(t+h,x)),\theta((t+h)+k,x))}{k} \\ = 0, \quad \text{by prop. } (ii) \text{ of transitions, with 't' } := t + h, \text{ 'h' } := k \end{cases}$$

$\square$

Proposition 2. *Property A holds whenever θ_2 and $\mathbb{O}_1$ come from the same space of transitions, whether they be (Borel) structuring, shape, or morphological transitions on $K \in \mathcal{K} (\mathbb{R}^n)$.*

Proof. For structuring transitions, $t (h\theta_2 + \mathbb{O}_1) + x = th\theta_2 + t\mathbb{O}_1 + x = th\theta_2 + h\mathbb{O}_1 + x = ht\theta_2 + h\mathbb{O}_1 + x = h (t\theta_2 + \mathbb{O}_1) + x$. For shape transitions, let $\theta_2 = \vartheta_\phi$. Then $t (h\theta_2 + \mathbb{O}_1) + K = t\vartheta_{h\phi} + K = th\vartheta_\phi + K = h\vartheta_{t\phi} + K = h (t\theta_2 + \mathbb{O}_1) + K$. For morphological transitions, let $\theta_2 = \vartheta_\Phi$. Then $t (h\theta_2 + \mathbb{O}_1) + K = t\vartheta_{h\Phi} + K = th\vartheta_\Phi + K = h\vartheta_{t\Phi} + K = h (t\vartheta_\Phi + \mathbb{O}_1) + K$. $\square$

Proposition 3. *Property B holds whenever θ_1, θ_2, and $\mathbb{O}$ come from the same space of transitions, whether they be (Borel) structuring, shape, or morphological transitions on $K \in \mathcal{K}(\mathbb{R}^n)$.*

Proof. For structuring transitions, $t(h\theta_2 + \theta_1) + K = th\theta_2 + t\theta_1 + K = th\theta_2 + t\mathbb{O} + t\theta_1 + K = t(h\theta_2 + \mathbb{O}) + t\theta_1 + K$. For shape transitions, let $\theta_1 = \vartheta_\phi$, and $\theta_2 = \vartheta_\psi$. Then $t(h\theta_2 + \mathbb{O}) + t\theta_1 + K = t(h\vartheta_\psi + \vartheta_0) + t\vartheta_\phi + K = th\vartheta_\psi + t\vartheta_\phi + K = t(h\vartheta_\psi + \vartheta_\phi) + K = t(h\theta_2 + \theta_1) + K$. The proof for morphological transitions is similar to that of shape transitions. □

Remark 4. *Property C holds for (Borel) structuring, shape, and morphological transitions acting on a member of $\mathcal{K}(\mathbb{R}^n)$ whenever the first and second transitions come from the same class of transitions by the definition of multiplication of Minkowski sums by a constant in each of these classes.*

We now turn to a technical statement that calculates a specific mutation.

Lemma 5 (Q). *Let $g : [0,T] \to E$ be such that $g, \overset{\circ}{g}$ are mutable. Let*

$$k(t) = t\left(\frac{t}{2}\overset{\circ\circ}{g}(0) + \overset{\circ}{g}(0)\right) + g(0), \ \overset{\circ\circ}{g}(0) = \theta_2, \overset{\circ}{g}(0) = \theta_1$$

We assume here properties A and B. Then $\overset{\circ}{k}(t) \ni p(t) = t\theta_2 + \theta_1$.

Proof. Fix t. We need to show:

$$\lim_{h \to 0} \frac{d(k(t+h), hp(t) + k(t))}{h} = 0.$$

First we use (S), (A) and (B) to manipulate $k(t+h)$. Then we use (S), (A) and (B) to manipulate $hp(t) + k(t)$. Finally we compare and calculate the limit. On the one hand we

calculate:

$$
\begin{cases}
k(t+h) = (t+h)\left[\frac{t+h}{2}\theta_2 + \theta_1)\right] + x \\[2ex]
= (t+h)\left[\frac{h}{2}\theta_2 + \frac{t}{2}\theta_2 + \theta_1\right] + x \qquad (S) \\[2ex]
= (t+h)\left[\frac{h}{2}\theta_2 + \frac{t}{2}\theta_2 + \mathbb{O}\right] + (t+h)\,\theta_1 + x \qquad (B) \\[2ex]
= \left[\frac{h^2}{2}\theta_2 + h\mathbb{O}\right] + \left[\frac{th}{2}\theta_2 + h\mathbb{O}\right] + (t+h)\left[\frac{t}{2}\theta_2 + \theta_1\right] + x \qquad (S) \\[2ex]
= h\left[\frac{h}{2}\theta_2 + \mathbb{O}\right] + h\left[\frac{t}{2}\theta_2 + \mathbb{O}\right] + (t+h)\left[\frac{t}{2}\theta_2 + \theta_1\right] + x \qquad (A).
\end{cases}
$$

On the other we compute:

$$
\begin{cases}
[p(t)](h, k(t)) = h[t\theta_2 + \theta_1] + t\left(\frac{t}{2}\theta_2 + \theta_1\right) + x \\[2ex]
= h[\frac{t}{2}\theta_2 + \frac{t}{2}\theta_2 + \theta_1] + t\left(\frac{t}{2}\theta_2 + \theta_1\right) + x \qquad (S) \\[2ex]
= h\left(\frac{t}{2}\theta_2 + \mathbb{O}\right) + h\left(\frac{t}{2}\theta_2 + \theta_1\right) + t\left(\frac{t}{2}\theta_2 + \theta_1\right) + x \qquad (B) \\[2ex]
= h\left(\frac{t}{2}\theta_2 + \mathbb{O}\right) + (t+h)\left(\frac{t}{2}\theta_2 + \theta_1\right) + x \qquad (S)
\end{cases}
$$

Now we bound the relevant distance. Let

$$
\begin{cases}
\tau = \frac{h}{2}\theta_2 + \mathbb{O} \\[3ex]
\psi = h\left[\frac{t}{2}\theta_2 + \mathbb{O}\right] + (t+h)\left[\frac{t}{2}\theta_2 + \theta_1\right] + x
\end{cases}
$$

Then we have that

$$
\begin{cases}
d(k(t+h), hp(t) + k(t)) = d(h\tau + \psi, \psi) \\[2ex]
\leq h.C_1.d(\tau, 1) \\[2ex]
\leq h.C_1.C_2.h/2
\end{cases}
$$

for some constants C_1 and C_2. Hence, $\lim_{h\to 0} d(k(t+h), hp(t)+k(t))/h = 0$, as required. $\qquad\square$

We finally come to a statement about the second-order approximation of a path in a metric space.

Theorem 6 (Taylor-2). *If $g : [0, T] \to E$ is such that*

$$
\begin{cases}
i) \ g \ \textit{mutable} \\
\\
ii) \ \mathring{g} : [0, T] \to \Theta(E) \ \ \textit{mutable} \\
\\
iii) \ \mathring{\mathring{g}}(t) \ \ \textit{is Lipschitz}
\end{cases}
$$

then $\exists$ constant $C \ \forall \ t$ such that $d\left(g(t), t\left(\frac{t}{2}\mathring{\mathring{g}}(0) + \mathring{g}(0)\right) + g(0)\right) \le Ct^3$.

Proof. $k(t) = t\left(\frac{t}{2}\mathring{\mathring{g}}(0) + \mathring{g}(0)\right) + g(0)$.

$$
d\left(g(t), t\left(\frac{t}{2}\mathring{\mathring{g}}(0) + \mathring{g}(0)\right) + g(0)\right) \le C_* t \cdot d_\Lambda\left(\mathring{g}(t), p(t)\right)
$$

$\square$

for a constant C_* by Lemma M (10), and $p(t)$ is just the first-order Taylor expansion of $\mathring{g}(t)$ about 0, so that

$$
C_* t \cdot d_\Lambda\left(\mathring{g}(t), p(t)\right) \le C_* C_{**} t^3
$$

for a constant C_{**}. Letting $C = C_* C_{**}$ finishes the proof.

We next highlight the full Taylor expansion in Mutational Spaces.

2.3   THE FULL TAYLOR THEOREM

Notation 1. *For $n \in \mathbb{N}$, we denote the nth mutation of a mutable function f by $\overset{(n)}{f}$.*

Theorem 2. *If $g : [0, T] \to E$ is such that*

$$
\begin{cases}
i) \ \overset{(i)}{g} \ mutable \ for \ i \in \{0, \ldots, n-1\} \\[2em]
ii) \ \overset{(n)}{g} \ Lipschitz
\end{cases}
$$

then, assuming axiom C, there exists a constant C for all t such that

$$
d\left(g(t), \sum_{i=0}^{n} \frac{t^i}{i!} \overset{(i)}{g}(0) \right) \le C t^{n+1}
$$

Proof. We proceed by induction on n. The case where $k = 1$ and $k = 2$ are done. Suppose that the Taylor expansion holds for $k = n - 1$. Again, by (10), we have, for a constant C^* that

$$
d\left(g(t), \sum_{i=0}^{n} \frac{t^i}{i!} \overset{(i)}{g}(0) \right) \le C^* t \cdot d_\Lambda\left(\overset{\circ}{g}(t), \sum_{i=1}^{n} \frac{t^{i-1}}{(i-1)!} \overset{(i)}{g}(0) \right)
$$

and, by the induction hypothesis, we have that

$$
d_\Lambda\left(\overset{\circ}{g}(t), \sum_{i=1}^{n} \frac{t^{i-1}}{(i-1)!} \overset{(i)}{g}(0) \right) \le C^{**} t^n
$$

so let $C = C^* C^{**}$ and we are done. $\qquad \square$

3.0 APPLICATIONS OF MUTATIONAL ANALYSIS TO NUMERICAL METHODS

Three applications of second transitions and second mutations are given below. First, we work out the Mutational Midpoint Method, then, we use properties A, B, and C to derive the Mutational Heun Method, and verify the correctness of Mutational Runge-Kutta methods more generally.

3.1 MIDPOINT AND HEUN METHODS

Theorem 1. *Let $(E, \Theta(E))$ be a mutational space, $y : [0, T] \to E$ continuous for some $T \in \mathbb{R}$, $f : E \to \Theta(E)$ be a continuous function, $\overset{\circ}{y} \ni f$, $g : \Theta(E) \to \Theta(\Theta(E))$ be such that $\overset{\circ}{f} \ni g$, and suppose, for a fixed t, that $y(t) = y_n$ has a second-order Taylor expansion, that is, $d\left(y(t+h), h\left(\frac{h}{2}g(y_n) + f(y_n)\right) + y_n\right) \leq Ch^3$. Define the Mutational Midpoint Method by:*

$$y_{n+1} = hf\left(\frac{h}{2}f(y_n) + y_n\right) + y_n$$

Then $d\left(y(t+h), y_{n+1}\right) \leq C'h^3$.

Proof. By (9)

$$\begin{cases} d\left(h\left(\frac{h}{2}g(y_n) + f(y_n)\right) + y_n, hf\left(\frac{h}{2}f(y_n) + y_n\right) + y_n\right) \\ \\ \leq C_1 h \cdot d\left(\frac{h}{2}g(y_n) + f(y_n), f\left(\frac{h}{2}f(y_n) + y_n\right)\right) \end{cases}$$

26

but $\frac{h}{2}g\left(y_n\right) + f\left(y_n\right)$ is just the first-order Taylor expansion of $f\left(\frac{h}{2}f\left(y_n\right) + y_n\right)$ about $f\left(y_n\right)$, and so

$$d\left(\frac{h}{2}g\left(y_n\right) + f\left(y_n\right), f\left(\frac{h}{2}f\left(y_n\right) + y_n\right)\right) \leq C_2 h^2$$

and thus

$$\begin{cases} d\left(y\left(t+h\right), y_{n+1}\right) \leq d\left(y_n, h\left(\frac{h}{2}g\left(y_n\right) + f\left(y_n\right)\right) + y_n\right) \\ \\ +d\left(h\left(\frac{h}{2}g\left(y_n\right) + f\left(y_n\right)\right) + y_n, hf\left(\frac{h}{2}f\left(y_n\right) + y_n\right) + y_n\right) \\ \\ \leq Ch^3 + C_1 C_2 h^3 \end{cases}$$

for constants C, C_1, C_2. $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ $\square$

Proposition 2. *Let $\left(E, \Theta\left(E\right)\right)$ be a mutational space, $y : [0, T] \to E$ be a continuous function for some $T \in [0, \infty)$, $f : E \to \Theta\left(E\right)$ be a Lipschitz function with Lipschitz constant Λ, $\overset{\circ}{y} \ni f$, $g : \Theta\left(E\right) \to \Theta\left(\Theta\left(E\right)\right)$ a continuous function such that $\overset{\circ}{f} \ni g$, and suppose that $y\left(t\right)$ has a second-order Taylor expansion $d\left(y\left(t+h\right), h\left(\frac{h}{2}g\left(y_n\right) + f\left(y_n\right)\right) + y_n\right) \leq Ch^3$. Define the Mutational Heun Method by*

$$y_{n+1} = \frac{h}{2}f\left(hf\left(y_n\right) + y_n\right) + \frac{h}{2}f\left(y_n\right) + y_n$$

Furthermore, suppose that axioms B and C hold. Then $d\left(y\left(t+h\right), y_{n+1}\right) \leq C'h^3$.

Proof. First, it can be shown that

$$d\left(\frac{h}{2}f\left(hf\left(y_n\right) + y_n\right) + \frac{h}{2}f\left(y_n\right) + y_n, \frac{h}{2}f\left(f\left(t+h\right)\right) + \frac{h}{2}f\left(y_n\right) + y_n\right) \leq C_1 h^3$$

27

for some $C_1 > 0$. Next,

$$
\begin{cases}
h \left(\frac{h}{2} g \left(y_n \right) + f \left(y_n \right) \right) + y_n \\[2mm]
= h \left(\frac{h}{2} g \left(y_n \right) + \mathbb{O} \right) + h f \left(y_n \right) + y_n \quad (B) \\[2mm]
= h \left(\frac{h}{2} g \left(y_n \right) + \mathbb{O} \right) + \frac{h}{2} f \left(y_n \right) + \frac{h}{2} f \left(y_n \right) + y_n \quad (S) \\[2mm]
= h \left(\frac{h}{2} g \left(y_n \right) + \mathbb{O} \right) + h \cdot \frac{1}{2} f \left(y_n \right) + \frac{h}{2} f \left(y_n \right) + y_n \\[2mm]
= h \left(\frac{h}{2} g \left(y_n \right) + \frac{1}{2} f \left(y_n \right) \right) + \frac{h}{2} f \left(y_n \right) + y_n \quad (B) \\[2mm]
= \left[\frac{h^2}{2} g \left(y_n \right) + \frac{h}{2} f \left(y_n \right) \right] + \frac{h}{2} f \left(y_n \right) + y_n \quad (C) \\[2mm]
= \frac{h}{2} \left[h g \left(y_n \right) + f \left(y_n \right) \right] + \frac{h}{2} f \left(y_n \right) + y_n \quad (C)
\end{cases}
$$

Finally, we see that

$$
\begin{cases}
d \left(y \left(t + h \right), y_{n+1} \right) \leq d \left(y \left(t + h \right), h \left(\frac{h}{2} g \left(y_n \right) + f \left(y_n \right) \right) + y_n \right) \\[2mm]
+ d \left(h \left(\frac{h}{2} g \left(y_n \right) + f \left(y_n \right) \right) + y_n, \frac{h}{2} f \left(f \left(t + h \right) \right) + \frac{h}{2} f \left(y_n \right) + y_n \right) \\[2mm]
+ d \left(\frac{h}{2} f \left(f \left(t + h \right) \right) + \frac{h}{2} f \left(y_n \right) + y_n, \frac{h}{2} f \left(h f \left(y_n \right) + y_n \right) + \frac{h}{2} f \left(y_n \right) + y_n \right) \\[2mm]
\leq C h^3 + d \left(h \left(\frac{h}{2} g \left(y_n \right) + f \left(y_n \right) \right) + y_n, \frac{h}{2} f \left(f \left(t + h \right) \right) + \frac{h}{2} f \left(y_n \right) + y_n \right) + C_1 h^3 \\[2mm]
= C h^3 + d \left(\frac{h}{2} \left[h g \left(y_n \right) + f \left(y_n \right) \right] + \frac{h}{2} f \left(y_n \right) + y_n, \frac{h}{2} f \left(f \left(t + h \right) \right) + \frac{h}{2} f \left(y_n \right) + y_n \right) + C_1 h^3 \\[2mm]
\leq C h^3 + C_2 h \cdot d \left(\left[h g \left(y_n \right) + f \left(y_n \right) \right], f \left(f \left(t + h \right) \right) \right) + C_1 h^3, \ C_2 > 0 \quad (Lemma \ T) \\[2mm]
\leq C h^3 + C_2 C_3 h^3 + C_1 h^3 = C' h^3, \ C_3 > 0 \quad (Taylor - 1)
\end{cases}
$$

$\square$

These numerical methods are both given for single steps. It remains to show that the full method converges, given their single-step convergence.

We give a slight re–statement of the Cauchy–Lipschitz theorem and then derive a general theorem allowing us to show that a sequence of approximate solutions to a mutational equation converges to the exact solution. This improves over Najman's proof that the Euler Scheme of approximations is 'convergent' [24] because it provides exact estimates of the error, and because the entire sequence converges to the exact solution – not just a subsequence.

Theorem 3 (Modified Cauchy-Lipschitz). *Suppose f is Lipschitz with Lipschitz constant $\|f\|$, and skirted $\alpha = \sup_x \alpha(f(x)) < \infty$. Let $A = \alpha + \|f\|$. Let $x = x(t)$ be a solution of $\overset{\circ}{x}(t) \ni f(x(t))$ for $t \geq 0$. Let $y = y(t)$ be another mutable function. Then for any $t_{i+1} \geq t_i \geq 0$, and all $t \in [t_i, t_{i+1}]$*

$$d(x(t), y(t)) \leq e^{A(t-t_i)} d(x(t_i), y(t_i)) + \int_{t_i}^t e^{A(t-s)} d_\Lambda(f(y(s)), \overset{\circ}{y}(s)) \, ds.$$

Theorem 4 (Convergence of Approximate Solutions). *Suppose f, $\|f\|$, α and A are as above. Fix $T \geq 0$. Suppose there is a constant C, a constant $k \geq 1$, and for each $h > 0$ a map $x_h = x_h(t)$ on $[0, T]$ such that:*

   (i) $x_h(t)$ is mutable,

   (ii) $x_h(0) = x_0 = x(0)$ and

   (iii) there is a partition $0 = t_0 < t_1 < \cdots < t_N = T$ of $[0, T]$ with $|t_{i+1} - t_i| \leq h$ for all i, such that

$$\int_{t_i}^{t_{i+1}} e^{A(t_{i+1}-s)} d_\Lambda(f(x_h(s)), \overset{\circ}{x}_h(s)) \, ds \leq Ch^{k+1}.$$

Then there is a constant D such that

$$\sup_{t \in [0,T]} d(x(t), x_h(t)) \leq Dh^k.$$

Thus the x_h's converge uniformly on $[0, T]$, in order k, to the exact solution x of $\overset{\circ}{x}(t) \ni f(x(t))$.

Proof. Take any $t \in [0, T]$. Then $t \in [t_i, t_{i+1}]$ for some i. We show, by induction on i, that there is a constant D such that $d(x(t), x_h(t)) \leq Dh^k$ – as required.

Case $t \in [t_0, t_1]$: Then apply the Modified Cauchy–Lipschitz Theorem (3), noting that $d(x(t_0), x_h(t_0)) = 0$, by hypothesis, along with condition (iv), to get:

$$d(x(t), x_h(t)) \leq Ch^{k+1}.$$

Case $t \in [t_1, t_2]$: Apply (3) over $[t_1, t_2]$ and use the estimate $d(x(t_1), x_h(t_1)) \leq Ch^{k+1}$ given by the previous case to get:

$$d(x(t), x_h(t)) \leq Ch^{k+1}e^{Ah} + Ch^{k+1}$$

Inductively, we get

Case $t \in [t_{N-1}, t_N]$: By (3) and the previous case:

$$d(x(t), x_h(t)) \leq (e^{Ah})^{(N-1)}Ch^{k+1} + \cdots + Ch^{k+1}.$$

Thus, irrespective of which subinterval $[t_i, t_{i+1}]$ t is in, we have:

$$
\begin{cases}
d(x(t), x_h(t)) \leq Ch^{k+1}\left(1 + e^{Ah} + \cdots (e^{Ah})^{(N-1)}\right) \\
\leq Ch^{k+1}\frac{(e^{Ah})^N - 1}{e^{Ah} - 1} \\
= h^k\left(C(e^{\frac{T}{h}Ah} - 1)\frac{h}{e^{Ah} - 1}\right) \\
\leq Dh^k
\end{cases}
$$

$\square$

Lemma 5. *With the notation of the previous theorems, condition (iv) is satisfied if:*

$$\sup_{t \in [t_i, t_{i+1}]} d_\Lambda(f(x_h(t)), \overset{\circ}{x}_h(t)) \leq Bh^k,$$

for some constant B (independent of h etc.).

Proof. The integral of (iv) is bounded as follows:

$$
\begin{cases}
\int_{t_i}^{t_{i+1}} e^{A(t_{i+1}-s)} d_\Lambda(f(x_h(s)), \mathring{x}_h(s))\, ds \leq Bh^k \int_{t_i}^{t_{i+1}} e^{A(t_{i+1}-s)}\, ds \\[3em]
\leq Bh^k \frac{e^{Ah}-1}{A} \\[3em]
\leq Ch^{k+1}
\end{cases}
$$

for some constant C (independent of h etc.). $\qquad\square$

3.2 EXPLICIT RUNGE-KUTTA METHODS

The Heun method of the last section is a second order version of a family of approximation methods called the Runge-Kutta methods. Let $(E, \Theta(E))$ be a first mutational space, $g : [0, T] \to E$ mutable, and $f : [0, 1] \times E \to E$ such that $\mathring{g} \ni f$. We can define a sequence of Runge-Kutta methods of increasing order by induction. For example, let $g^{(1)}$ be obtained by the Euler Method, a first order Runge-Kutta method. That is, $g_{n+1}^{(1)} = hb^{(1)} f(t_n, g_n) + g_n$. Then define $g^{(m+1)}$ as the $(m+1) - st$ order Runge-Kutta method by $g_{n+1}^{(m+1)} = hb^{(m+1)} f\left(t_n + c^{(m+1)}h, g_n^{(m)}\right) + g_n^{(m+1)}$, where $b^{(i)}, c^{(i)} \in \mathbb{R}$ for all i. Of course, choosing different $b^{(i)}$ and $c^{(i)}$ produce different families of RK methods. Nevertheless, for fixed $b^{(i)}$ and $c^{(i)}$, the following result is quite useful.

Theorem 1. *For a RK method $g_n^{(m)}$, $d\left(g(t+h), g_{n+1}^{(m)}\right) \leq Ch^{m+1}$.*

Proof. By induction:

$m = 1, 2 :$ Euler and Heun methods have already been done.

$m = k + 1 :$ We have

$$
\begin{cases}
d\left(g(t+h), g_{n+1}^{(k+1)}\right) = d\left(g(t+h), hb^{(k+1)} f\left(t_n + c^{(k+1)}h, g_n^{(k)}\right) + g_n^{(k+1)}\right) \\[2em]
\leq Dh \cdot d\left(g(t+h), f\left(t_n + c^{(m+1)}h, g_n^{(k)}\right)\right) \leq Dh \cdot D^* h^k
\end{cases}
$$

utilizing a basic property of transitions and the induction hypothesis, respectively. $\qquad\square$

31

4.0 STOCHASTIC ANALYSIS ON SUBSET SPACES

In this section, we begin a modest measure theory for spaces of subsets. Our goal is to use this theory for several applications. Two applications will be discussed in this chapter: Stochastic Mutational Equations in the sense of "convergence in measure" and general parameter estimation of subsets. In the next chapter, we will take a look at a particular biological model that is a primary motivation for this stochastic extension.

4.1 GAUSSIAN INTEGRALS

For simplicity of illustration, we will only consider the set of all subsets of subsets of $\mathbb{R}$, in other words, $2^{2^{\mathbb{R}}}$. However, the theory is similar when replacing $\mathbb{R}$ with any set X. For an adequate treatment of Gaussian integrals, see [3]. The next two definitions will serve as finite dimensional templates for a measure we define on $2^{2^{\mathbb{R}}}$.

Definition 1. *The one-dimensional Gaussian integral is*

$$G\left(A\right) := \int_{A} \frac{e^{-x^2} dx}{\sqrt{2\pi}}, \ A \subseteq \mathbb{R}$$

and the n-dimensional Gaussian integral is

$$G_n\left(A\right) := \int_{A} \frac{e^{-x^2} dx}{\sqrt{(2\pi)^n}}, \ A \subseteq \mathbb{R}^n$$

Since, in our infinite-dimensional integrals, we concern ourselves only with integrating over functions (as opposed to more general relations), we restrict ourselves to situations where A is rectangular. Thus, $G_n(A)$ can actually be written as the product of one-dimensional integrals. That is

$$G_n(A) := (2\pi)^{-\frac{n}{2}} \prod_{i=1}^{n} \int_{A_i} e^{-x_i^2} dx, \ A_i \text{ is the projection of } A \subseteq \mathbb{R}^n \text{ onto the } nth \text{ coordinate}$$

and this yields some intuition in progressing to an infinite-dimensional version of Gaussian integration.

We begin by considering $[a, b] \subset \mathbb{R}$, and giving a definition of a measure on $\mathbb{R}^{[a,b]}$.

Definition 2. *The measure $\mu_{[a,b]}$ on $\mathbb{R}^{[a,b]}$ is the unique measure such that for any finite partition $\{t_i\}, i = 1, \ldots n$ of $[a, b]$ such that $a \leq t_1 < t_2 < \cdots < t_n \leq b$, the projection of $\mu_{[a,b]}$ onto $\mathbb{R}^{\{t_i\}}$ is G_n. We can denote this as follows:*

$$\mu_{[a,b]}(A) := \prod_{x \in [a,b]} \int_A dG_1(x), \ A \subseteq \mathbb{R}$$

where dG_1 is the one-dimensional Gaussian measure, in the sense of the aforementioned integral. The fact that $\mu_{[a,b]}$ is, in fact, unique can be found in [12]. This measure can be extended to a measure $\mu_{\mathbb{R}}$ by taking the limit of closed intervals increasing in size.

While $\mu_{[a,b]}$ is interesting enough, we take our methods one step further. Consider the set $\mathbb{R}^{[a,b]^{[c,d]}}$. For two elements $g, h \in \mathbb{R}^{[a,b]^{[c,d]}}$, we say that $g \prec h$ iff $g(x(t)) \leq h(x(t))$ for all $x \in [a, b]^{[c,d]}$ and $t \in [c, d]$. Let us now define a measure on $\mathbb{R}^{[a,b]^{[c,d]}}$.

Definition 3. *The measure $\mu_{[a,b]^{[c,d]}}$ on $\mathbb{R}^{[a,b]^{[c,d]}}$ is the unique measure such that for any finite partition $\{x_i(t_j)\}$, $i = 1, \ldots, n$, $j = 1, \ldots m$ of $[a,b]^{[c,d]}$ such that $c \le t_1 < \cdots < t_m \le d$ and $a \preceq x_1 \prec \cdots \prec x_n \preceq b$ in the sense of $(\prec, \mathbb{R}^{\mathbb{R}})$, the projection of $\mu_{[a,b]^{[c,d]}}$ onto $\mathbb{R}^{\{x_i(t_j)\}}$ is G_{mn}. We can denote this as follows:*

$$\mu_{[a,b]^{[c,d]}}(A) := \prod_{x \in [a,b] \times [c,d]} \int_A dG_1(x), \ A \subseteq \mathbb{R}$$

Now we can extend an infinite dimensional measure to any finite multipower. For the set of all subsets of subsets of $\mathbb{R}^n$, and $A \subseteq \{0,1\}$, we will use

$$\mu\left(2^{2^{[a,b]^n}}, A\right) := \prod_{x \in \{0,1\} \times [a,b] \times \{0,\ldots n-1\}} \sum_A n(x)$$

and, whenever we wish to replace $[a,b]$ with $\mathbb{R}$, we will use

$$\mu\left(2^{2^{\mathbb{R}^n}}, A\right) := \lim_{\substack{a \to -\infty \\ b \to \infty}} \mu\left(2^{2^{[a,b]^n}}, A\right) = \prod_{x \in \{0,1\} \times \mathbb{R} \times \{0,\ldots,n-1\}} \sum_A n(x)$$

whenever the limit exists. As a technical point, whenever the one-dimensional projections are measures on subsets of $A \subseteq \mathbb{Z}$, we replace the Gaussian measure with a measure γ such that $\gamma(A) < \infty$. As another technical point, we should mention that the $\sigma-$algebra for these measures are the cylindrical $\sigma-$algebras discussed in [12].

4.2   APPLICATIONS

Let $\left(2^{2^{\mathbb{R}^n}}, \mathcal{A}, \mu\right)$ be a measure space. Recall that, for $f, g \in 2^{\mathbb{R}^n}$, we have that $f \prec g$ iff $f(x(y)) < g(x(y))$ for all $x \in \mathbb{R}^n$ and all $y \in \{1, \ldots, n\}$. Define a metric on $2^{\mathbb{R}^n}$ by $d(f, g) = \mu([f, g])$, for $f \prec g$. Consequently, $\left(2^{\mathbb{R}^n}, d\right)$ is a metric space, and one can then turn it into a mutational space $\left(2^{\mathbb{R}^n}, \Theta\left(2^{\mathbb{R}^n}\right), d\right)$ by specifying a set of mutations $\Theta\left(2^{\mathbb{R}^n}\right)$. The effect of the Mutational Cauchy-Lipschitz Theorem on this mutational space is that solutions of stochastic mutational equations can be defined by *convergence in measure.*

Additionally, we can use this pair of metric space and measure space on the hyperspace to do non-parametric estimation on a general mutational equation. Let $x(\cdot) : [0, T] \to 2^{\mathbb{R}^n}$ be the solution to a mutational equation $\overset{\circ}{x}(t) \ni f(x(t))$, where $f : 2^{\mathbb{R}^n} \to \Theta\left(2^{\mathbb{R}^n}\right)$ is Lipschitz and skirted, and $\overset{\circ}{x} : [0, T] \to 2^{\Theta\left(2^{\mathbb{R}^n}\right)}$ is a mutation. We construct a measure space $\left(2^{\Theta\left(2^{\mathbb{R}^n}\right)}, T, \tau\right)$ and associate it with the metric space $\left(\Theta\left(2^{\mathbb{R}^n}\right), \delta\right)$ in such a way that $\delta(h, k) = \tau([h, k])$, for $h, k \in \Theta\left(2^{\mathbb{R}^n}\right)$, $h \prec k$. Now we define the maximum likelihood estimate of f.

Definition 1. *The maximum likelihood estimate of f given $f \in A$, $x(t)$ and $\overset{\circ}{x}(t)$ is the f that minimizes the function*

$$MLE(f) := \inf_{\substack{f \in Lip\left(2^{\mathbb{R}^n}, \Theta\left(2^{\mathbb{R}^n}\right)\right) \cap A \\ f \ skirted}} \inf_{\xi \in \overset{\circ}{x}(t)} \delta(\xi(t), f(x(t)))$$

for almost all $t \in [0, T]$.

The intuitive interpretation for metrics of the type d and δ above is that two elements are similar to each other if the probability that another element can be inserted between them is rather low.

We can extend this construction into a more general setting. Let $\left(2^{\Theta(K)}, \mathcal{K}, \kappa\right)$ be a measure space, $(K, \Theta(K), \delta)$ a mutational space, and $(\Theta(K), d)$ a totally ordered metric space such that, for $a, b \in K$, $d(a, b) = \kappa([a, b])$, whenever $a \leq b$. Let $\overset{\circ}{y}(t) \ni g(y(t))$, where $y : [0, T] \to K$, and $g : K \to \Theta(K)$ is Lipschitz and skirted, and $\overset{\circ}{y} : [0, T] \to 2^{\Theta(K)}$ is a mutation. Then we can define the following.

Definition 2. *The maximum likelihood estimate of g given $g \in B$, $y(t)$ and $\mathring{y}(t)$ is the g that minimizes the function*

$$MLE(g) := \inf_{\substack{g \in Lip(K,\Theta(K)) \cap B \\ g \ skirted}} \inf_{\gamma \in \mathring{y}(t)} \delta\left(\gamma(t), g(y(t))\right)$$

5.0 STOCHASTIC MUTATIONAL ANALYSIS AND CANCER MODELLING

We consider here two models of combined tumorigenesis and angiogenesis. That is, we are interested in cancer growth in the presence of surrounding vascular growth. The first model will be (mostly) concrete, with a sample implementation left to the appendix. The second model will be largely abstract, but illustrative of the flexibility of modelling with mutational analysis.

5.1 FIRST MODEL (JUNIOR GRADE)

For the first model, we operate, for the sake of simplicity, in the square $[0,1] \times [0,1]$. Fix $T \in [0,\infty)$. We will work with the mutational space

$$\left(\mathcal{K}\left([0,1]^2\right) \times \mathcal{K}\left([0,1]^2\right), LIP\left([0,1]^2,[0,1]^2\right) \times LIP\left([0,1]^2,[0,1]^2\right), D \right)$$

where $LIP\left([0,1]^2,[0,1]^2\right)$ is the set of Lipschitz closed convex processes on the square, and D is the product Hausdorff metric 1.2. Representing a tumor will be the mutable function $C : [0,T] \to \mathcal{K}\left([0,1]^2\right)$, and representing the network of small vessels will be $V : [0,T] \to \mathcal{K}\left([0,1]^2\right)$, also mutable. Our product transition will depend on what each shape looks like at a particular time t. That is:

$$\left(\overset{\circ}{C} \times \overset{\circ}{V} \right)(t) \ni (\theta \times \tau)\left[C(t) \times V(t)\right]$$

37

and we now define θ and τ. The transition θ will represent the mutation of the tumor, and τ represents the mutation of the vasculature. They are as follows:

$$
\begin{cases}
\theta\left(h, C\left(t\right)\right) = \bigcup_{x \in C(t)} x \\[2em]
+ h p_1 \left\{ d\left(x, ME\left(V\left(t\right)\right)\right) \wedge c \right\} \left[ME\left(V\left(t\right)\right) - x\right] \\[2em]
+ \frac{h p_2}{d(x, ME(V(t))) + \kappa} B \\[2em]
\tau\left(h, V\left(t\right)\right) = \bigcup_{y \in E[V(t)]} \int_0^1 y \\[2em]
+ h q_1 d\left(y, C\left(t\right)\right) \alpha \left[ME\left(C\left(t\right)\right) - y\right] d\alpha
\end{cases}
$$

where p_1 and q_1 are rates of "chemotaxis", a way of one shape being able to seek its way to another, which naturally happens in living organisms by way of producing and emitting chemicals, c and κ are positive constants required to bound growth, p_2 is a proliferation constant for tumor expansion, ME is a function that returns the barycenter of a set, E is the function of the set of endpoints of V. In the appendix, we set $|E| = 1$, so that we are dealing with one vessel, but one can model V as a star formation, with any fixed finite number of line segments stemming from one point. Both transitions are continuous, as they are unions of continuous selections. The function d is simply the Euclidean set to point distance. Finally, the set B is the closed unit ball in $\mathbb{R}^2$.

5.2 SECOND MODEL (UTILITY GRADE)

The second model is a strict extension of the first. The tumor and vessel set functions will exhibit much more complex behavior, as probabilistic phenomena are added. We will now allow centrally necrotic tumor tissue, de novo synthesis of blood vessels by the tumor itself (as well as recruitment of blood vessels as in model 1), administration of antiangiogenic medication (via blood vessels), and metastatic growth (tumor sets that are disconnected).

De novo synthesis of blood vessels and metastasis will require a very different mutational space from that of model 1. Continuity issues with disconnected sets and the probabilistic description force us to adopt a mutational structure more like the ones in the Probability Measures section. Because of the complexity of this model, transitions will not be displayed in the complete closed form, as they were in model 1. Rather, this model description serves the purpose of highlighting the true power of the Mutational Analysis method over the deterministic or stochastic PDE method of dynamical system modelling.

Let us now operate in $[0,1]^3$ with $T \in [0, \infty)$. Let $\left(2^{2^{[0,1]^3}}, \mathcal{A}, \mu \right)$ be a measure space, and $\left(2^{[0,1]^3}, 2^{[0,1]^3}, d \right)$ be an ordered mutational space with the usual ordering, such that, whenever $f, g \in 2^{[0,1]^3}$ with $f \leq g$, $d(f,g) = \mu([f,g])$. In similar fashion to the previous model, we have $C, V : [0,T] \rightarrow 2^{[0,1]^3}$, which are both mutable. We will use the same mutational equation above

$$\left(\overset{\circ}{C} \times \overset{\circ}{V} \right)(t) \;\ni\; (\theta \times \tau)\left[C(t) \times V(t) \right]$$

except that we will now describe, narratively, both θ and τ.

The transition θ will take four actions with different probabilities. With probability a_1, it will grow each point $x \in C(t)$ radially, essentially adding a scaled closed unit ball around it,

$$\left(\bigcup_{x \in C(t) \setminus V(t)} x + hp_1 B \right) \bigcup \left(\bigcup_{x \in C(t) \cap V(t)} x + \frac{h}{m(t)} B \right)$$

as above. The function $m(t)$ can be seen as a dosage of antiangiogenic medication at time t, retarding the growth of tumor in the vicinity of the treatment influx. With probability a_2, $C(t)$ will be replaced with

$$C(t) \setminus \left\{ \cup_{x \in C(t)} \overset{\circ}{B}(h,x) : d\left(x, [0,1]^3 \setminus C(t)\right) \geq M \right\}$$

where M is a real-valued random variable, bounded below by a constant $r > 0$, with a cumulative distribution function $F(x)$. In other words, central necrosis is activated with probability a_2. Note that only interiors are deleted, so that $\overset{\circ}{B}(0,x)$ is empty. With

probability a_3, if $C(t) \cap E(V(t))$, give the members of $E(V(t))$ a uniform distribution and draw randomly one endpoint. This corresponds to an "entry point" for the tumor. Then, take the drawn point as a starting point, and transfer all points of $V(t)$ within hs units of that endpoint over to $C(t)$. This is the equivalent of an invasion of solid tumor mass into a blood vessel. We shall not bother ourselves so much with the case where many small capillaries are bunched together. From an empirical standpoint, it is reasonable for a tumor mass to invade many close capillaries simultaneously. Finally, with probability $1 - a_1 - a_2 - a_3$, if $h \neq 0$, give the members of $[0,1]^3$ within h of $C(t)$ the uniform distribution, choose one point from that distribution, and add that point to $C(t)$. One may, instead, only consider points in space that are adjacent to blood vessels in the selection, if one is considering the vasculature the only method of metastasis.

Transition τ will be much simpler. Fix probabilities b_1 and b_2 so that $b_1 + b_2 < 1$. With probability b_1, the ends of all vessels will grow by hq_1, much like in the last model. With probability b_2, assign the uniform distribution to the entire vascular network, pick a point in the network, and designate that point as a new endpoint. Consequently, the vasculature will remain inactive with probability $1 - b_1 - b_2$.

It should be noted here that it is possible to recast the new model in closed form. The narrative serves to illustrate how flexible mutational models can be, and how much faster they can be realized than their PDE counterparts. One may suspect, in addition, that a PDE equivalent of this model is not possible, because of the frequent additions and deletions of points to each set evolutions.

Also note that θ and τ are continuous with respect to t by construction. This can be checked easily for all twelve event types. For illustration, the case for when the tumor and vasculature network both grow (with probability $a_1 b_1$) will be shown. It suffices to show, in this case, that whenever $h \to 0$, $d(\theta(h), \mathbb{O}) \to 0$. This distance is considered by measuring the absolute value of the characteristic function of the following set

$$\left[\left(\bigcup_{x \in C(t) \setminus V(t)} x + hp_1 B \right) \bigcup \left(\bigcup_{x \in C(t) \cap V(t)} x + \frac{h}{m(t)} B \right) \right] \setminus C(t)$$

and the fact that $h \to 0$ empties this set implies that its characteristic function tends to

an absolute value of zero, and we are done. That $h \to 0$ implies $d\left(\tau\left(h\right), \mathbb{O}\right) \to 0$ is clear.

6.0 CONCLUSION AND FUTURE DIRECTIONS

A substantial expansion of Mutational Analysis has been given in the current discussion. The discussion began with a review of key definitions, examples, results, and inferences of Aubin's initial work. Then, the first new item is an extension of the concept of mutation to higher orders. It is shown how interesting this extension is in its own right, and then its usefulness is highlighted in the study of second and higher order mutational numerical methods. The second new item is an extension of the the concept of mutation to stochastic mutations. This relies on already existing mathematics relating to the integration of functions on infinite dimensional spaces. This extension allows for a more robust application of mutational analysis to real world problems involving data. The biological examples of cancer evolution are displayed as an illustrative example to this end. Depending on the nature of application, there are several directions that one can travel in with respect to the new theories of the current work.

There has been much focus on the mathematical accuracy of approximations of mutational equations in this discussion, but little mention of computational speed. Part of the reasoning behind this comes from the fact that there is almost always a no-arbitrage trade off of one for the other. It is usually taken for granted that higher order numerical methods and/or larger domains will result in an slower speed of computation. It is also taken for granted that, for mutational equations on spaces that are not vector spaces, the number of computations required to obtain a satisfactory result is greatly reduced from that of an adequately approximate formulation in terms of equations that require vector space domains. That much is illustrated from the examples of shapes space equations given thus far. It would be interesting to find out which (non-vector-space) metric spaces with additional structure simplify computations enough to significantly increase computational speed.

Recently there has been a demand in engineering and science fields for multiscale modeling, or modeling of complex systems on multiple physical scales. This has been driven largely by the desire for a more systems-oriented approach to modeling [4]. Since mutational equations have the capability of considering several different types of evolutions simultaneously, it naturally supports multiscale modeling. Where Mutational Analysis may find a distinct advantage in multiscale modeling is the consideration of several shifting scales. It is not unreasonable to expect, from experimental data, either that exact scales are impossible to obtain, requiring approximate or probabilistic scales to suffice, or that the salient scales themselves are dynamic, and change in magnitude over time, or over some other range of attributes. Therefore, it may be a worthwhile project to determine what of Mutational Analysis finds value in describing such sliding scale systems.

On a more theoretical note, one recognizes Mutational Analysis, as it currently stands, as a theory of calculus on topological spaces. Then, one naturally asks the question, "Can this theory be applied to spaces more general than topological spaces?" There are several mathematical categories that can serve as probable generalizations. One such example is the category of approach spaces, where point-to-point distances are replaced (non-trivially) with point-to-set distances [21]. The resulting point-to-singleton set distances will generally not match up with the point-to-point distances of any metric. Another example is the category of convergence spaces, where one replaces a metric with a collection of local filters at each point in the space [21]. There is also a category of convergence-approach spaces that contains both convergence spaces and approach spaces as subcategories [22]. Finally, there is the category of Čech closure spaces, containing spaces with a simple preclosure operator [27]. This category contains both topological and pretopological spaces as subcategories.

BIBLIOGRAPHY

[1] Aubin, Jean-Pierre. "Mutational Equations in Metric Spaces". (1993) Set-Valued Analysis 1:3-46.

[2] Aubin, Jean-Pierre. "Mutational and Morphological Analysis: Tools for Shape Evolution and Morphogenesis". (1999) Birkhauser.

[3] Baaquie, Belal. "Quantum Finance". (2007) Cambridge.

[4] Bassingthwaighte, and J.B. Chizeck, and H.J. Atlas, L.E. "Strategies and Tactics in Multiscale Modeling of Cell-to-Organ Systems". (2006) Proceedings of the IEEE. 94(4):819-831.

[5] Billingsley, Patrick. "Convergence of Probability Measures". 2nd Ed. (1999) Wiley-Interscience.

[6] Columbo, Rinaldo and Guerra, Graziano. "Differential Equations in Metric Spaces with Applications". (2008) Working paper.

[7] Fabian, Marian and Habala, Petr and Hájec, Petr and Santalucía, Vicente Montesinos and Pelant, Jan and Zizler, Václav. "Functional Analysis and Infinite-Dimensional Geometry". (2001) Springer-Verlag.

[8] Goradia, A. Ning Xi Prokos, M. Zhiwei Cen Mutka, M. "Cooperative Multi-Target Surveillance using a Mutational Analysis Approach". (2005) July. Advanced Intelligent Mechatronics Proceedings. 940-945.

[9] Hajłasz, Piotr. "Sobolev spaces on an arbitrary metric space". (1996) Potential Anal. 5(4):403-415.

[10] Hajłasz, Piotr. "A new characterization of the Sobolev space". (2003) Studia Math. 159(2):263-275.

[11] Hajłasz, Piotr and Koskela, P. "Sobolev met Poincaré". (2000) Memoirs of the American Mathematical Society 145:688.

[12] Halmos, Paul. "Measure Theory". (1950) Van Nostrand.

[13] Heinonen, Juha. "Lectures on analysis on metric spaces". (2001) Universitext. Springer-Verlag. New York.

[14] Jain, R.K. "Antiangiogenic therapy for cancer: current and emerging concepts". (2005) Apr. 19(4):7-16.

[15] Kelley, John L. "General Topology" (1955) New York.

[16] Kerbel, R.S. "A Cancer Therapy Resistant to Resistance". (1997) Nature 390:335-336

[17] Lane, E. P. "Bitopological Spaces and Quasi-Uniform Spaces". (1967) Proceedings of the London Mathematical Society. 3(17):241-256.

[18] Lorenz, Thomas. "Evolution Equations in Ostensible Metric Spaces: Definitions and Existence". (2005a) Working paper.

[19] Lorenz, Thomas. "Evolution Equations in Ostensible Metric Spaces: Examples in Banach Spaces". (2005b) Working paper.

[20] Lorenz, Thomas. "Generalizing Evolution Equations in Ostensible Metric Spaces: Timed Right-Hand Sleek Solutions provide Uniqueness of 1st-order Geometric Examples." (2005c) Working paper.

[21] Lowen, R. "Approach Spaces: The Missing Link in the Topology-Uniformity-Metric Triad". (1997) Oxford.

[22] Lowen, E and Lowen, R. "A Quasitopos Containing CONV and MET as Full Subcategories". (1988) International Journal of Mathematics & Mathematical Sciences. 11(3):417-438.

[23] McKinnell, Robert G. and Parchment, Ralph E. and Perantoni, Alan O. and Damjanov, Ivan and Pierce, G. Barry. eds. "The Biological Basis of Cancer". 2nd Ed. (2006) Cambridge University Press.

[24] Najman, Laurent. "Euler Method for Mutational Equations". (1995) Journal of Mathematical Analysis and Applications. 196:814-822.

[25] Panasyuk, A I. "Quasidifferential Equations in a Metric Space". (1985) Differentsial'nye Uravneniya 21(8):1344-1353.

[26] Pervin, William J. "General Topology". (1964) Academic Press.

[27] Stadler, Peter F. "Genotype-Phenotype Maps". (2006) Preprint.

[28] Tabor, Jacek. "Differential Equations in Metric Spaces". (2002) Mathematica Bohemica 127(2):353-360.

[29] Thampuran, D. V. "Bitopological Spaces and Quasiuniformities". (1970) Manuscript.

[30] Thampuran, D. V. "Bitopological Spaces and Complete Regularity". (1970) Manuscript.

[31] Thampuran, D.V. "Quasiuniformization of Bitopological Spaces". (1970) Manuscript.

[32] Tuominen, Heli. "Characterization of Orlicz-Sobolev Spaces". (2007) Ark. Mat. 45(1)

APPENDIX

We have encoded a version of model 1 in the Python language in order to illustrate the ease of implementing spatial models describe in terms of mutational equations. While, in practice, a particular model becomes tied to a reference system of an author's choosing, much of the mutational framework can be encoded in an implementation-independent framework. Displayed below is the Python code used for both the Taylor-type approximations of the mutational equation used, as well as the elementary transitions and their compositions. At the end, an implementation of the script for evaluating a particular numerical method is provided.

Algorithm: Euler Method

```
def Euler_sequence(f,x0,h,N):
    xs=[x0]
    for i in range(1,N):
        xs.append(f(xs[i-1])(h,xs[i-1]))
    return xs
```

Algorithm: Midpoint Method

```
def Midpoint_sequence(f,x0,h,N):
    xs=[x0]
    xi=x0
```

```python
for i in range(1,N):

    y=f(xi)(h/2,xi)

    z=f(xi)(h/2,xi)

    xi=f(y)(h,z)

    xs.append(xi)

return xs
```

Algorithm: Heun Method

```python
def Heun_sequence2(f,x0,h,N):

    xs=[x0]

    xi=x0

    for i in range(1,N):

        y=f(xi)(h,xi)

        z=f(xi)(h/2,xi)

        xi=f(y)(h/2,z)

        xs.append(xi)

    return xs
```

Interface: Basic Geometric Operations

```python
def Union(ss):

    return reduce(lambda x,y : x|y, ss)

def disk(center,radius):

    K=int(radius)

    disk=set([center])

    for i in range(-K+1,K):

        for j in range(-K+1,K):

            cur_pt=(int(center[0]+i), int(center[1]+j))

            if distance(center,cur_pt)<= radius:

                disk.add(cur_pt)

    return disk

def line_segment(start,direction,length):
```

```python
        (sx,sy)=start
        (dx,dy)=direction
        len_d=sqrt(dx**2+dy**2)
        line=set([start])
        if (len_d != 0):
            for t in range(length):
                line.add( (sx+int(t*dx/len_d),sy+int(t*dy/len_d)) )
        return line


def cylinder(center,radius,height):
        K=int(radius)
        cylinder=set([center])
        for i in range(-K+1,K):
            for j in range(-K+1,K):
                cur_pt=(int(center[0]+i), int(center[1]+j), int(height))
                if distance(center,cur_pt)<= radius:
                    cylinder.add(cur_pt)
        return cylinder
def cube_segment(start,direction,length,height):
        (sx,sy)=start
        (dx,dy)=direction
        len_d=sqrt(dx**2+dy**2)
        line=set([start])
        if (len_d != 0):
            for t in range(length):
                line.add( (sx+int(t*dx/len_d),sy+int(t*dy/len_d),height) )
        return line
def vector_sum(x,y):
        return tuple(xi+yi for (xi,yi) in zip(x,y))
def add_vector2set(x,K):
```

return set(vector_sum(x,y) for y in K)

def int_scalar_product(a,x):

return tuple(int(a*xi) for xi in x)

def multiply_set_by_scalar(a,K):

return set(int_scalar_product(a,x) for x in K)

Interface: Flow-Based Transitions

def transition_from_scaled_flow(f):

return lambda h,K : Union([add_vector2set(x,f(h,x)) for x in K])

def MidPoint_transition_from_scaled_flow(f):

return lambda h,K : set(vector_sum(x,z) for x in K for y in f(h/2,x) for z in f(h,vector_sum(x,y)))

def Heun_transition_from_scaled_flow(f):

return lambda h,K : set(vector_sum(x,vector_sum(y,z)) for x in K for y in f(h/2,x) for z in f(h/2,vector_sum(x,int_scalar_product(2,y))))

Implementation: Euler Method

#initial condition is shape of cancer and vasculature

x0=(C0,V0)

#mutational equation: deriv((C(t),V(t))) in F((C(t),V(t)))

transitions are products of morphological transitions

defined from flows G and H

the flow G (resp H) defines for each h>0 and point x a compact, convex set

in this case a disk (resp a line segment)

from mutations.transitions.morphological import disk,

line_segment,transition_from_scaled_flow

from mutations.transitions.operations import product

need a parameter, c, for G, and d for H

c=320

d=250

```
maxgrowth=20
def F((C,V)):
    # the (scaled) flow G
    def G(h,x):
        dnp=D(V,d_2)(x)
        r=1
        if dnp != 0.0:
            r=min(c*h/dnp,maxgrowth) # capped dynamics
        return disk((0,0),r)
    # the (scaled) flow H
    def H(h,x):
        (dnp,np)=DD(C,d_2)(x)
        r=1
        if dnp != 0.0:
            r=min(d*h/dnp,maxgrowth) # capped dynamics
        start=(0,0)
        direction=(np[0]-x[0],np[1]-x[1])
        length=int(r)
        return line_segment(start,direction,length)
    # return the product of transitions from these 2 flows
    return product(transition_from_scaled_flow(G),
        transition_from_scaled_flow(H))
# We (approximately) solve the mutational equation using Euler's method
from mutations.soln_schemes.Euler import Euler_sequence
#from mutations.soln_schemes.Heun2 import Heun_sequence2
#from mutations.soln_schemes.Midpoint import Midpoint_sequence
#set step size and number of steps
#h=0.25
#N=5
h=0.33333
```

N=7

print "Calculate Euler sequence..."

CV=Euler_sequence(F,x0,h,N)