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Multi-Scale Modeling and Analysis of Left Ventricular Remodeling Post Myocardial Infarction: Integration of Experimental and Computational Approaches

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Abstract

Progressive remodeling of the left ventricle (LV) following myocardial infarction (MI) involves spatiotemporal interactions among multiple cell types and the extracellular matrix environment. Despite the extensive experimental studies designed to elucidate the regulatory mechanisms, there is a growing recognition that the complexity of LV remodeling precludes the efficient identification of early diagnostic indicators after myocardial infarction. Currently, systemic approaches are needed to reduce this complexity. Previous studies in other systems demonstrate that establishing a multi-scale analytical model of LV remodeling response to MI will likely help in the development of prognostic therapies. In this review, we discuss the current approaches used for mathematical modeling of the LV, advantages and disadvantages of the approaches, and methods used to validate these models.

Keywords: mathematical model, left ventricular remodeling, extracellular matrix, inflammation, outcome prediction, model validation

1. Introduction

A myocardial infarction (MI) occurs when a coronary artery becomes totally closed off, resulting in the loss of oxygen to the downstream myocardium (a process termed ischemia). Following MI, the left ventricle (LV) undergoes a spectrum of responses at the gene and protein levels that are represented clinically as changes in LV size, shape, and function [1]. LV remodeling encompasses many alterations, including LV wall thinning, LV dilation, and infarct expansion; inflammation and necrotic myocyte resorption; fibroblast accumulation and scar formation; and endothelial cell activation and neovascularization [2, 3]. LV remodeling is also influenced by variations in leukocyte response (neutrophil and

macrophage influx), blood pressure and volume, molecular changes (neurohormonal activation and cytokine production), and extracellular matrix responses (fibrosis and activation of proteases, particularly the matrix metalloproteinases (MMPs) and serine proteases) [4]. In addition, pre-existing conditions such as increased age, diabetes, or the use of drugs such as angiotensin converting enzyme inhibitors and β adrenergic receptor inhibitors can influence remodeling outcomes. Basically, LV remodeling after MI is a complex wound healing response that involves the dynamic spatiotemporal interactions between the various cell types and the acellular components.

2. Rationale for Mathematical Modeling of LV Remodeling

While research over the past 30 years has accumulated vast amounts of experimental data and has greatly improved our understanding of LV remodeling post-MI, this knowledge has not been translated to the effective identification of early diagnostic indicators that can accurately predict the post-MI patient who is at high risk to develop heart failure. This is evidenced by the fact that long-term heart failure survival post-MI has not been improved, and a five year mortality rate of 50% persists [5]. MI is the number one cause of heart failure, accounting for 70% of all heart failure cases [6]. Therefore, using mathematical modeling approaches to understand how the LV progresses during the post-MI response may provide mechanistic insight into LV remodeling that can be used to develop novel therapeutic strategies.

The complexity of LV remodeling and the inability of one experiment to all-inclusively examine all parameters (or even examine only the most critical parameters) make it impossible to experimentally study this problem at the whole systems level. What is needed is to separate the system into its constituent parts and recombine these parts together to understand the whole system.

This superposition approach is successful if the system is linear and the tested variables are independent from each other. LV remodeling, however, involves many components with coupled feedback loops and nonlinear saturating kinetic responses. The remodeling process exhibits “emergent behavior”, which means that remodeling displays system dynamics that are not attributable to any specific component but rather to the whole system. Therefore, analyzing individual components in isolation is not likely to reveal the full spectrum of system behavior. Indeed, there is growing recognition that complex biological progression should be examined based on spatiotemporal interactions [7-14]. Spatiotemporal interactions can be characterized in terms of mathematical relations built on the mechanism of the system and validated by experimental data. In particular, the availability of high-throughput quantitative data and improved computing power have recently made mathematical modeling of LV remodeling more feasible.

In this review, we will focus on the temporal profiles of biochemical components in the LV post-MI in mice, current mathematical modeling methods that can be used to develop models, and methods to validate the mathematical model with experimental data.

3. Temporal Profiles of LV remodeling

MI occurs when there is a sustained interruption of the blood supply to the heart, leading to rapid death of the myocytes in the affected part of the cardiac wall. Since cardiac myocytes

are post-mitotic cells, the necrotic myocytes cannot be replaced with cells with similar characteristics, as occurs in other wound healing systems such as the skin and liver. Instead, the infarct area is repaired with granulation tissue that matures into a scar. Progressive LV remodeling post-MI can be divided into four phases: the necrotic phase immediately after MI, the acute inflammatory response phase from day 1-7, the formation of granulation tissue phase (1-3 weeks), and the remodeling phase (> 3 weeks) [15, 16].

3.1 Cellular changes

In normal mouse myocardium, the Baudino laboratory has shown that myocytes, fibroblasts, vascular smooth muscle cells, and endothelial cells accounts for 56%, 27%, 10%, and 7% of total cell numbers, respectively [17]. Post MI, myocytes die and the major cell types are (myo)fibroblasts, endothelial cells, and inflammatory cells (including neutrophils, macrophages, and lymphocytes).

Necrotic phase: myocytes

As early as six hours post-MI, myocyte death is apparent. Apoptosis is believed to be responsible for the early myocyte death in the first 6 hrs to 8 hrs post-MI, whereas necrosis is more of a secondary event that occur 12 hrs to 4 days after myocardial infarction [18]. This secondary event may be caused by the fact that the majority of apoptotic cells cannot be consumed or phagocytosed by neighboring cells. In reaction to this, an inflammatory response is initiated within the infarct region. The influx of leukocytes is the hallmark of the inflammatory response phase.

Inflammatory response phase: neutrophils, macrophages, and lymphocytes

The early inflammatory response after myocardial infarction takes place within 12 - 16 hours after the onset of ischemia (in the absence of reperfusion). Neutrophils are the first immune response cells to arrive at a site of infection. Neutrophils produce enzymes such as elastase and matrix metalloproteinase (MMPs) that allow inflammatory cells to migrate into the infarct tissue to remove the necrotic myocytes. The number of neutrophils migrated to the infarct region peaks at 1-3 days after MI and is significantly declined by day 5 post-MI [19]. After releasing storage granule components, neutrophils undergo apoptosis and are subsequently removed by macrophages.

Macrophages follow the neutrophils influx and have a strong phagocytic function to remove necrotic myocytes and apoptotic neutrophils. Activated macrophages are differentiated from peripheral blood monocytes [21]. Macrophage proliferation is not a significant component, since previous studies have shown that <5% of macrophages undergo mitotic division [20, 21]. Macrophages infiltrate into the infarct from days 2-7 and peak at day 4, indicating that the acute inflammatory response occurs within 4 days and is marked by the removal of necrotic tissue and repair. Macrophage infiltration gradually decreases after day 14, even though macrophage densities are still higher than control at day 28 post-MI [19]. Macrophages do not die locally in the scar tissue but emigrate to the lymph node system for disposal [22]. Macrophages play a pivotal role in the transition between inflammation response and fibrotic phase stimulated by macrophage secretory product, transforming growth factor β (TGF- β).

Lymphocyte infiltration peaks at 1 week post-MI and gradually decreases, suggesting that the transformation from an acute to chronic inflammation begins within 1 week. Of these

three leukocyte cell types, the lymphocyte is the least understood in terms of post-MI responses.

Formation of granulation tissue phase: fibroblasts

Two to 3 days post-MI, the granulation tissue begins to form around the border of the infarct region. This tissue is rich in inflammatory cells, fibroblasts, and blood vessels.[16] During this phase, fibroblasts start ECM deposition, which increases the myocardial tensile strength. Myofibroblasts first appear in the infarct at day 3 and remain at high levels through day 28 post-MI. The major source of fibroblasts is the resident cell [23] and the circulating fibrocyte is a minor source. Previous study has shown that proliferation rate of fibroblasts in C57BL/6J mice was $15.4\pm 1.1\%$ 4 days post-MI, declined to $4.1\pm 0.6\%$ by 1 week, progressively slowed to $0.2\pm 0.6\%$ after 2 weeks, and $0.03\pm 0.1\%$ after 4 weeks [24]. Our lab also demonstrated that fibroblast proliferation rates decrease by day 28 post-MI, indicating that fibroblast densities may reach a saturation point. It has also been shown that myofibroblasts replicated at the border of the infarct zone migrate inward at day 4, more centrally at one week, sporadically at 2 weeks, and ceased by 4 weeks [24, 25]. In addition, our previous studies have shown that fibroblast growth rate, secretion rate, and migration are modulated by TGF- β .

Remodeling phase: myofibroblasts

Approaching 3 weeks post-MI, the cell number in the granulation tissue starts to decrease. This is the first hallmark of the remodeling phase of infarct wound healing. Apoptosis plays an important role in the decreasing cell numbers. However, a unique feature of the cardiac scar, compared with skin scars, is the persistent presence of fibroblasts. Fibroblasts have been visualized in human post-MI scars as late as 17 years after the MI. This implies that fibroblasts in the cardiac scar are crucial mediators of remodeling and may be less prone to apoptosis than in other types of scars.

Angiogenesis: endothelial cells

Angiogenesis is the process of generating new capillary blood vessels, which restores blood supply to the heart. The angiogenesis phase overlaps with the inflammatory and granulation tissue phases, and improves cell survival during these phases. Activation and proliferation of endothelial cells are essential steps in angiogenesis. It has been shown that continuous endothelial cell activation increases angiogenesis [26]. Virag and colleagues have shown that proliferation rates of endothelial cell in C57BL/6J mice are $2.9\pm 0.5\%$ at 4 days post-MI, decline to $0.7\pm 0.1\%$ by 1 week, and remain at low levels of $0.2\pm 0.1\%$ after 2 weeks and $0.4\pm 0.3\%$ after 4 weeks [24]. Endothelial cells, therefore, are important contributors to post-MI remodeling.

3.2 Cytokine and Growth Factor changes post-MI

Multiple cytokines have been measured at the gene and protein levels. IL-1 β levels increase within 3 hours, remain high at 6-12 hours, and decrease by 24 hours post-MI in C57/BL6J mice [27]. TNF- α levels are elevated on days 1 and 2, significantly decline by day 7, and gradually decrease to baseline levels by day 28. IL-6 shares a similar temporal profile with TNF- α [28]. IL-10 is elevated on day 1, peaks on day 2 and shows sustained increases at day

7, and declines significantly on day 28. TGF- β 1 mRNA expression significantly increases at day 3 and gradually decreases from days 7 to 28, even though their expression levels are still higher than controls [29]. In addition, Schnoor and colleagues have recently demonstrated that macrophages contain mRNAs for a large number of collagens (particularly collagen VI) and fibronectin [30].

3.3 ECM changes

The cardiac extracellular matrix (ECM) provides the environment for cell migration, proliferation, adhesion, and cell-to-cell signaling. Cardiac ECM includes collagens (types I, III, IV, V, and VI); matricellular proteins (tenascins, thrombospondins, and secreted protein acidic and rich in cysteine); proteoglycans (lumican, versican, and biglycan); glycosaminoglycans (hyaluronic acid and dermatan sulfate); and glycoproteins (fibronectin, laminins, periostin, fibromodulin, and vitronectin) [31]. Extracellular proteases include serine proteases and MMPs that are present either bound to the ECM, in various cell types, or in circulating blood. In addition, the development of LV remodeling has been linked to the discontinuity and disruption of the supporting collagen network within in the ECM [32]. Therefore, cardiac ECM is a vital component of LV remodeling.

Collagen III levels are elevated 3 days post-MI in rat. The increase in collagen III is followed by an increase in collagen I production to increase the tensile strength of the infarct tissue [33].

The major source of collagen in the heart is the fibroblast. In addition, post-MI fibroblasts expressing collagen mRNA are always co-localized with lymphocytes and macrophages in rats [34, 35], implicating inflammation as a necessary component of the fibrotic response. Fibroblasts in the post-MI LV are primarily myofibroblasts that have differentiated from resident fibroblasts or from infiltrating fibrocytes. Whether the source (resident or infiltrating) yields myofibroblasts with different characteristics has not been examined.

Multiple MMPs and tissue inhibitors of metalloproteinases (TIMPs) have been shown to be altered post-MI in both human and animal studies. MMPs -1, -2, -3, -7, -8, -9, -12, -13, -14 and TIMPs -1 and -2 levels increase, while TIMP-3 and TIMP-4 levels decrease post-MI [36-38]. Specifically, MMP-9 levels are elevated from days 1-3, decrease after day 3 while still holding high levels at day 7 [39-41]. MMP-3 is one of the key factors related to MMP-9 activation. MMP-3 expression is up-regulated 2 days post-MI, reaches the maximum at 4 days and remains up regulated throughout the 14-day [42].

Developing a Multi-scale Mathematical Model of LV Remodeling

Temporal profiles of cellular function and ECM changes reveal that dynamic interactions during LV remodeling process involve cardiac function, cellular function, protein expression, and gene expression. Accordingly, a full spectrum of the LV remodeling may only be obtained by integrative knowledge on genes, protease, cells, tissue and the whole organ.

A pyramid modeling structure is shown in Figure 1 to illustrate the possible layers of a complete model of the heart. The top layer includes LV changes in structure, function, and geometry, which can be regulated by the 2nd layer components including mechanical, electrical, chemical signals, and surgery/wound exercise. Components in the 2nd layer can be further related with tissue components and cellular functions regulated by biochemical molecules and genes in the 3rd layer. Mathematical modeling focusing on the upper layer of the pyramid are simplified composite models to characterize the system features, while the

under lying modular models are complicate, but capable of providing more detailed predictions. However, there is always a tradeoff between model simplicity and adaptability of the mathematical model.

Most of the current models for the heart are structural models or cellular models, due to the richness of related experimental data. Previous studies have reported structural model focusing on mechanical properties [43, 44] and cellular model focusing on electrophysiology [45-49]. Our team has recently developed the first model for scar formation post-MI, which demonstrated the interactions among macrophage, fibroblasts, MMP-9, TGF- β_1 and collagen.

For a cellular model built on properties of proteins, it is possible for the model to reach down to genetic level by reconstructing the effects of particular mutations. Examples using Markov models of cardiac sodium channel have been studied by Rudy and colleagues [50]. In addition, the cellular model can also reach up to a whole organ model including both the electrical and mechanical behaviors of heart [51, 52]. We predict that incorporation of molecular/genetic models, cellular models and structural/functional models will be one of the most exciting prospects of computational biology in the coming years.

4. Modeling Methodology

Various modeling techniques, such as nonlinear dynamics, physical chemistry, and stoichiometric network analysis have been applied to describe the underlying framework of biological systems [53]. Dependent on the attempting problem, different modeling methods can be taken to describe the system.

Ordinary differential equations (ODE) methods have been used to represent continuous, deterministic systems for temporal mechanics. ODE modeling takes a population view of a system rather than modeling the stochastic behavior of individual proteins or molecules. The variables of the ODEs generally represent average concentrations of the components. Partial differential equations (PDEs) are the spatial counterpart of ODE and have been widely used to model spatially restricted reactions in a system, taking into account diffusion processes in the chemical reactions.

ODE and PDE models have strength on elucidating the quantitative spatial and temporal interactions in the system. ODE/PDE models also integrate nonlinearity terms easily, matching with the embedded nonlinearity of the biological system. In addition, control design, stability and sensitivity analysis techniques of ODE based model have been well developed, which make the ODE based model an excellent tool to analyze and predict the effects of interventions beyond the range of available data. Our team and other researchers have analyzed stability of ODE based model [54, 55]. Parameter sensitivity analysis has been presented by Marino and colleagues [56]. Given a system dynamics $F(\theta_i, x_j), i = 1, 2, \dots, n$, and $j = 1, 2, \dots, m$ with parameters θ_i and variables x_j , Sensitivity of parameter θ_i is defined as $S_{\theta_i}^F = \frac{\partial F}{\partial \theta_i} \frac{\theta_i}{F}$. A negative $S_{\theta_i}^F$ means increasing parameter θ_i will decrease the value of function F at this specific point; a positive means increasing parameter θ_i will increasing the value of function F. The maximum absolute value of the sensitivity function tells us which parameter affects the system dynamics most. However, ODE methods require exact knowledge of reaction rate and concentrations of the biochemical factors, which is hard to acquire in some biological systems. In case of the non-

precise measurement of the parameters, parameter sensitivity analysis is generally desired for system performance and validation of the parameters calls for parameter search in a given space to optimize the fitting between computational predictions and experimental data.

Non-ODE methods have also been widely applied to model biological systems where the actions of individual elements of a system, rather than the population behavior, is of interest [57]. Stochastic methods have been applied to model the individual behavior of molecules and represent variability in the overall behavior of a system [58]. Stochastic method has the advantages on handling imprecise data, where concentrations of molecules are represented by relative levels rather than exact values in ODE methods.

Agent-based modeling method has also been developed based on the rules and mechanisms of behavior of individual component of a system [59]. Agents represent the system components which share the same mechanism identified by experimental results. The mechanisms are expressed as a series of conditional (if-then) statements and computer programs are written to describe the rules of behavior. Agent-based methods provide an easy way to translate basic Scientific data to model. However, it requires extensive computational power to simulate large numbers of agents of a real system. In addition, agent-based model is very difficult to validate and calibrate with experimental data.

There are also other model methods, such as Petri nets, process algebra (PEPA) and SBML-based graphical model, but ODE/PDE model, stochastic model, and agent-based model are the most commonly applied techniques. The strength and weakness of the aforementioned modeling methods are summarized in Table 1.

5. Mathematical Modeling Procedure

A well established mathematical model is easy to understand, reproduce, and test. A modeling standard for reproducibility has been presented by Dr. Bassingwaite [60]. A recommended modeling procedure is summarized as following steps.

- 1) Identify the functionality of the model. A modeler has to determine the scope of the model and make realistic assumptions to develop the model at this step.
- 2) Determine the structure and content of the model. A modeler will identify variables of the ODE/stochastic model (concentrations, mass, etc) or agents for the agent-based model, units of the variables, parameters of the model (reaction rate, growth rate), inputs/outputs (ODE model), or nodes/edges (stochastic model).
- 3) Quantify the mathematical relation based on physical chemistry laws, mass balance, charge balance, energy balance for ODE model, evolutionary probability for stochastic model, and behavior rules for agent-based model. For example, the mass balance equation for a compartmental modeling can be written as
Mass change = Sources - Sinks.
- 4) Verify the mathematical relation based on unitary balance of equations, variables and parameters.
- 5) Develop software to compute the mathematical model and compare the numerical solution with available analytical solution.
- 6) Validate the mathematical model.

5.1 Validation of the Mathematical model

The crucial component of a model is the ability of the model to accurately reflect the real-world process being modeled. Validation of the model, therefore, is a necessary step to evaluate the similarity. Validation of mathematical model focuses on two aspects: 1) assumptions made during the model development, and 2) behavior of the model. Validation of an assumption can be addressed by explicit statement of conditions and rules to implement the model. All models represent some degree of abstraction of the system, assumptions of the model determines the degree of abstraction. Therefore, clarity of the assumptions is the key for model validation.

Behavior of the model can be validated by comparing the behavior of the model with real-world experimental data. When the behavior of the model matches with the experimental data, the model is validated for the particular case. Mismatch of the model behavior and experimental data requires further investigation on either model structure or parameters calibration.

Practically, validation of the mathematical model includes the following aspects. 1) Confirm that defined initial and boundary conditions (generally based on the assumptions) are appropriate to the physiology and physical chemistry data. 2) Compare computational and experimental results to see if the two sets of values are compatible. This comparison is made by determining the fitting error between the computational and experimental results. 3) Optimize and document parameters with respect to the fitting errors. 4) Test predictions of the model with new experiments.

A good model will satisfy a desired fitting of experimental results. If the lack of fitting is caused by structural defects, a more extensive literature search is needed to find the missing regulatory mechanisms. To minimize the fitting error caused by parameter calibration, parameter optimization is needed to minimize the fitting error. The most commonly applied technique is least squared based optimization which minimize the value of $\sum_{i=1}^N e_i^2$, where e_i is the fitting error at i th fitting point and N denotes the total fitting points. Thus, a desirable parameter setting of the model will be obtained with respect to a given fitting error.

6. Conclusion

In summary, progressive LV remodeling following MI involves spatiotemporal profiles of cellular, protein, and genetic components. Although this review focuses on the modeling of LV remodeling post-MI, it is worth mentioning that modeling techniques have been widely applied to other gene regulatory networks, metabolic pathways, cells, and organs [49, 61-66]. However, integration of multi-scale mathematical models into the whole organ model still needs intensive investigation. It is anticipated that integrated computational and experimental approaches will greatly facilitate researchers in their everyday experimental work and shed insight on regulatory mechanisms of LV remodeling as well as other disease processes.

7. Acknowledgements

We acknowledge funding to MLL from NIH (R01 HL075360), the American Heart Association (GIA 0855119F), and the Morrison Trust, and funding to YJ from NSF (EEC-0649172), NIH (1SC2HL101430), and AT&T foundation.

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Figure Legends

Figure 1. Pyramid structure of LV remodeling post-MI. Progressive LV remodeling includes tissue components, cell functions, protein interactions and gene regulation. A multi-scale mathematical model should weave the components into a model for the whole system.

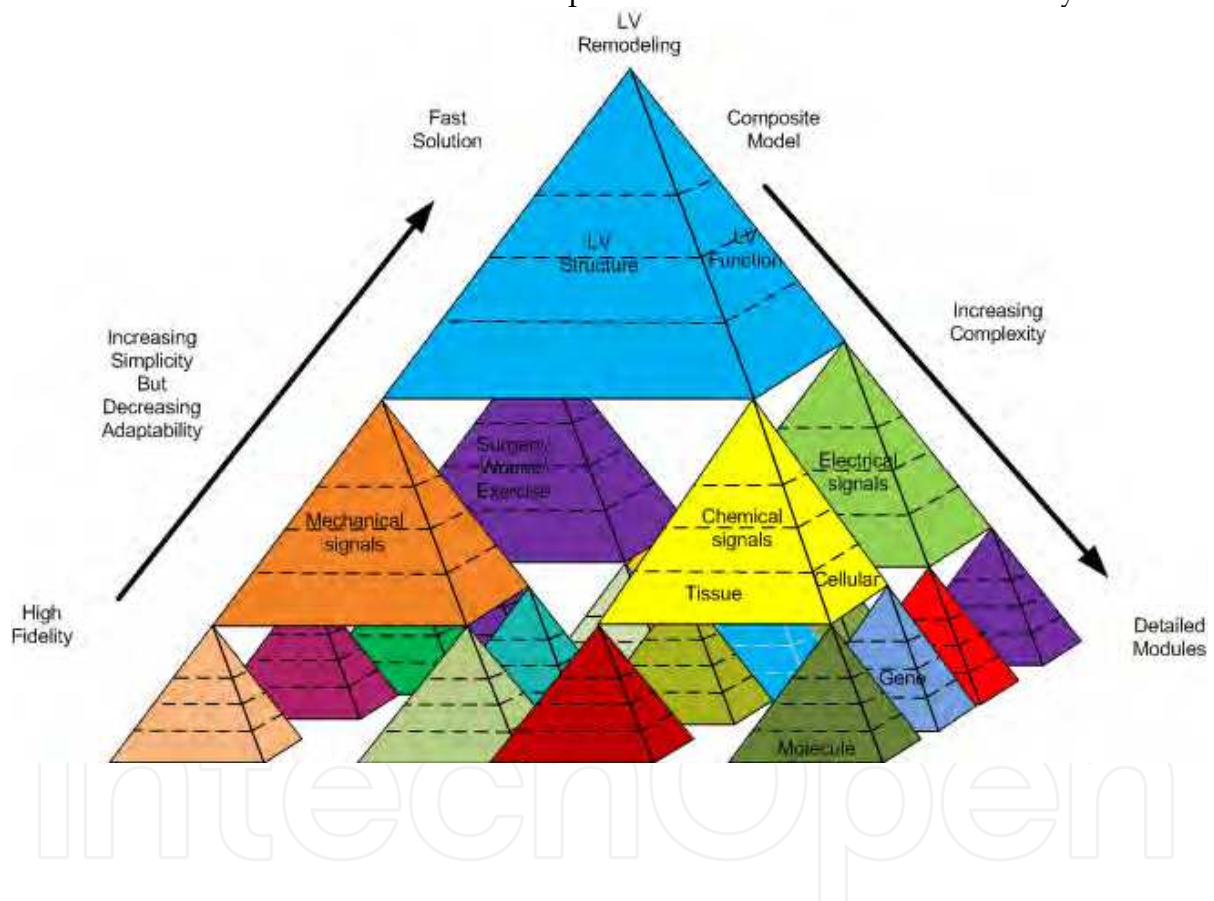


Table Legends

Modeling Technique	Strengths	Weaknesses
Ordinary/partial differential equation model	Continuous and deterministic model for exact values with biophysical meaning Characterizes temporal and spatial interactions Well developed stability analysis techniques Provides good prediction on unmeasured data	Requires exact knowledge of the system and precise measurement of the parameters
Stochastic model	Probability based model Robust to imprecise parameters	Provides relative levels instead of exact values
Agent-based model	Easy to translate from experimental knowledge to system behavior	High requirement on computational power Hard to validate the model and calibrate parameters

Table 1. Summary of the strengths and weaknesses of different mathematical methods.

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Application of Machine Learning

Edited by Yagang Zhang

ISBN 978-953-307-035-3

Hard cover, 280 pages

Publisher InTech

Published online 01, February, 2010

Published in print edition February, 2010

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How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Yufang Jin Ph.D. and Merry L. Lindsey Ph.D. (2010). Multi-Scale Modeling and Analysis of Left Ventricular Remodeling Post Myocardial Infarction: Integration of Experimental and Computational Approaches, Application of Machine Learning, Yagang Zhang (Ed.), ISBN: 978-953-307-035-3, InTech, Available from: <http://www.intechopen.com/books/application-of-machine-learning/multi-scale-modeling-and-analysis-of-left-ventricular-remodeling-post-myocardial-infarction-integrat>

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