Theguinea pig HF proteome exhibited classic biosignatures of cardiac HYP, left ventricular dysfunction, fibrosis, cellular degeneration, inflammation and extravasation. Fatty acid metabolism, mitochondrial transcription/translation factors, and other mitochondrial processes, were downregulated. Processes/proteins upregulated in HF include fibrillogenesis, extracellular matrix remodeling, cytoskeletal proteins, the unfolded-protein response, and acute phase inflammation markers. Among metabolites, downregulation of acyl-carnitines was observed in HYP, while fatty acids accumulated in HF. Levels of the TCA cycle metabolite, citrate, and the potent inhibitor, 2-methylcitrate, increased upon transition from HYP to HF. Among transcripts, downregulation of repolarizing $K^+$ channels, SERCA2a, phospholamban and ryanodine receptor was noted, and upregulation of mRNAs for cyclic-nucleotide gated hyperpolarization-activated channels and TRPC6.
The biosignature of decompensation in the guinea pig HF/SCD model parallels prior rodent models but spotlights metabolic bottlenecks. Fatty acid use is likely abrogated by impaired mitochondrial import and oxidation, while compensation by glycolytic flux is predicted to be impaired, along with TCA cycle dysfunction and accumulation of inhibitors (e.g. citrate). Pathway analysis suggests avenues for metabolic therapy beyond PPAR activation.

**3090-Pos Board B520**
**Cellular Signaling Networks Function as Generalized Wiener-Kolmogorov Filters to Suppress Noise**
**Michael Hinczewski**[1], Devarajan Thirumalai[2].
[1]Department of Physics, Case Western Reserve University, Cleveland, OH, USA, [2]Institute for Physical Science and Technology, University of Maryland, College Park, College Park, MD, USA.
Cells process and transmit information about their environment through complex signaling cascades. The accurate transmission of the information is crucial for normal function, with defects in the cascades linked to a host of cancers. As in many designed communications systems, these biological circuits must cope with noise that inevitably corrupts the signal. How to efficiently filter noise, to reconstruct the best estimate of the input, has been a key problem in engineering. One of the great advances in this area was a mathematical framework developed by Norbert Wiener and Andrey Kolmogorov during the Second World War, originally inspired by the need to filter noise in the targeting of anti-aircraft systems. Remarkably, we show that cells effectively implement the same mathematical solution encoded within the chemical reaction network of a kinase phosphatase push-pull loop, a basic unit of signaling pathways. To demonstrate this, we generalize the ideas of Wiener and Kolmogorov to deal with some of the challenges that arise in the biological context, including signaling through discrete changes in molecular populations, and the highly nonlinear relation between input and output. We provide mathematically rigorous bounds on the performance of biochemical noise filters, and highlight features of the system relevant for optimizing filter efficiency, encoded in a single, measurable, dimensionless parameter. Our theory, which describes noise control in a large class of signal transduction networks, is also useful both for the design of synthetic biochemical signaling pathways, and the manipulation of pathways through experimental probes like oscillatory input.

**3091-Pos Board B521**
**To Grow is not Enough: The Impact of Cell Response Time on Fitness**
**Nash Rochman**, Fangwei Si, Sean Sun.
Johns Hopkins, Baltimore, MD, USA.
Recent results showing the magnitude of fluctuations in individual cell division times to be highly concerted across widely varying cell types and environmental conditions have been difficult to explain with current molecular cell cycle models. Here we present a phenomenological model for the regulation of cellular division time distributions determining both bulk growth rate and ensemble fluctuations. A cellular ''fitness'' function is proposed which incorporates not only growth rate, which is maximized when fluctuations are minimized, but also ensemble response time to environmental stimulus which decreases for increasing fluctuations. Single cell division data is collected on a population of isogenic cells subjected to varying environmental stimuli and compared to the model. Our findings suggest that even cells exhibiting exponential growth do not optimize their ''fitness'' through growth rate alone, but also response time.

**3092-Pos Board B522**
**Bcl-2 Overexpression Stimulates Glycolysis and Lactic Fermentation in a Bax-Dependent Fashion**
Bushra Mahmood, Jessica Wilson, Miriam Ahmad, Patricia Olino, Justin King, **Laurent Dejean**.
Chemistry, California State University of Fresno, Fresno, CA, USA.
It is now well established that shifts in energy metabolism are associated with cancer development and progression. The most studied of these phenomena is the Warburg effect, which corresponds to an increase of anaerobic glycolysis vs mitochondrial oxidative phosphorylation to produce energy for cellular processes. However, the mechanisms related to these metabolic switches are still a matter of debate. Bcl-2 family proteins contain both pro- (e.g. Bax), and anti-apoptotic (e.g. Bcl-2) members which are respectively encoded by tumor suppressors and proto-oncogenes. Up-regulation of the anti-apoptotic proteins Bcl-2 has been associated with Non-Hodgkin's lymphoma; and certain studies indicate that Bcl-2 plays a role in the regulation of energy metabolism. However, the molecular players involved in this regulation are still to be defined. We recently observed that Bcl-2 overexpression led a significant increase of both glucose consumption and lactate production rates in a mouse pro-lymphocyte B cell line. This phenomenon was associated with a stimulation of the lactate dehydrogenase (LDH) enzyme specific activity; and a Bcl-2-mediated increase of the expression of the LDH-A subunit. Also, this phenotype was strongly attenuated if a Bcl-2 mutant of interaction with Bax (Bcl-2-G145E) was overexpressed instead of native Bcl-2. These data suggest that Bcl-2 expression levels may play an active role in the stimulation of lactic fermentation commonly observed in blood cancer cells; and that this effect may be dependent to the ability of Bcl-2 to physically interact with Bax.

**3093-Pos Board B523**
**Human Adipose Cell Response to Insulin: Analysis of Cellular Switch-Like Transformations and Distributions**
Vladimir A. Lizunov[1], **Paul S. Blank**[1], Karin G. Stenkula[2], Monica Skarulis[3], Samuel Cushman[4], Joshua Zimmerberg[1].
[1]NICHD, Laboratory of Cellular and Molecular Biophysics, National Institutes of Health, Bethesda, MD, USA, [2]Experimental Medical Sciences, Lund University, Lund, Sweden, [3]Diabetes, Endocrinology, and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA, [4]Experimental Diabetes, Metabolism, and Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA.
Insulin resistance is associated with decreased glucose transporter-4 (GLUT4) translocation in adipose cells and muscles in response to insulin. Here we quantified, per cell, insulin's effects on GLUT4 storage vesicle (GSV) tethering and fusion in adipose cells from human subjects with varying insulin sensitivity index (SI). Basal GSV tethering and fusion rates were distributed unimodally and did not vary significantly with SI. In contrast, after a maximal insulin challenge, both tethering and fusion rates were bimodally distributed, with two distinct subpopulations; the first subpopulation was indistinguishable from the basal distribution, while the second corresponded to a normal insulin response. Importantly, the fraction of cells in the two-subpopulations were strongly correlated with donor subject SI. These data suggest that the loss of systemic SI is not due to a gradual decrease in the insulin response of all cells, but rather an increase in the fraction of cells that switch off their insulin response. This observed heterogeneity may be an important consideration in modeling the cellular transitions and systemic changes associated with the onset of Type II diabetes. Thus, isolated human adipose cells, when treated with high concentrations of insulin, exist in either the basal or fully insulin-stimulated state, and population dose response curves reflect the proportion of adipose cells in these two distinct states.

**3094-Pos Board B524**
**Accelerating Systems Biology Computation: Enhanced Sampling of Spatially Realistic Stochastic Models using the Weighted Ensemble Approach**
**Rory Donovan**.
University of Pittsburgh, Pittsburgh, PA, USA.
We apply the ''weighted ensemble'' (WE) simulation strategy, previously employed in the context of molecular dynamics and spatially homogeneous chemical kinetics simulations, to a number of three dimensional spatially resolved stochastic systems-biology models. WE is relatively easy to implement, does not require extensive hand-tuning of parameters, does not depend on the details of the underlying simulation algorithm, and can facilitate the unbiased sampling of extremely rare events.
We study three systems of varying complexity and structure: a toy model in an artificial geometry with ~103 diffusing molecules, a spatially realistic cellular model with ~106 molecules, and a spatially realistic neuromuscular junction model with time-varying rate ''constants'' containing ~106 molecules. We are able to speed up the sampling of key events by many orders of magnitude and obtain unbiased estimates of event probabilities. Data is obtained using the publicly available ''WESTPA'' implementation of WE, which orchestrates MCell kinetic Monte Carlo trajectories of the various models.