

## Multi-scale Mathematical Modeling to Support Drug Development

D. A. Nordsletten<sup>1</sup>, B. Y. Yankama<sup>2</sup>, R. Umeton<sup>3</sup>, V. S. Ayyadurai<sup>2</sup>, and C. F. Dewey, Jr.<sup>2</sup>

<sup>1</sup>King's College, U. London, London, United Kingdom, <sup>2</sup>Massachusetts Institute of Technology, Cambridge, MA, <sup>3</sup>Sapienza University, Rome, Italy

It is widely recognized that major improvements are required in the methods currently being used to develop new therapeutic drugs [1]. The time from initial target identification to commercialization can be 10 to 14 years and incur a cost in the hundreds of millions of dollars. Even after substantial investment, only 30-40% of the candidate compounds entering clinical trials are successful. We propose that multi-scale, separable mathematical pathway modeling can be used to decrease time required to bring candidate drugs to clinical trial and increase the probability that they will be successful in humans.

**Introduction:** The two key needs of a multi-scale approach to drug development are: (a) predictive models of the biological pathways; and (b) recycling of information between the different processing steps in the drug development pipeline. Examination of these two needs leads to three specific multiscale problems that require immediate attention: (a) a massively complex scale of calculation; (b) simulation of multiple time scales; and (c) volume-length scales to support spatial inhomogeneity in addition to global reactions [4]. The requirements for multiple time scales and spatial scales are discussed, and new computational paradigms are identified to address the increased complexity of modeling. We identify problems derived from managing the complexity, which surface in the time-scales, and propose solutions involving adaptive time steps among a set of parallel ODEs. We conclude that complexity and maintenance issues are best served by maintaining individual pathways that can be federated on demand to achieve quantitative predictions of drug efficacy and toxicity.

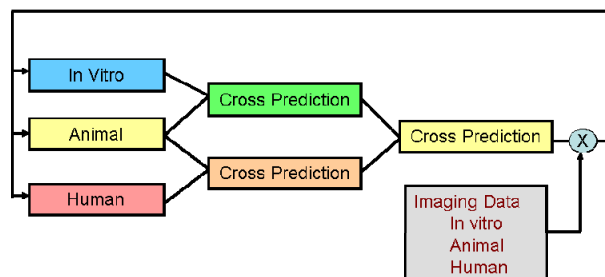
**Requirements for Drug Development:** A single monolithic computational model predicting the complete behavior of a single cell in a specified extracellular environment could involve  $10^3$  molecular pathways and  $10^5$  ordinary differential equations. Although the number of curated quantitative pathways is growing rapidly, at this time an assembly of 10-50 pathways might be available today in developing any specific therapeutic drug combination. What is required for the process is an automated means of maintaining and updating the wealth of information about the pathway reactions and the components with which they react. This feedback is shown in Fig. 1 which depicts our proposal for a general cross--prediction platform.

**Complexity:** Looking at a cell as a complete monolithic model  $M$ , working with independent component pathways can be seen as an integration of  $N$  partially observed models,  $M_1..M_N$ . Federating a complete, simulable  $M$  requires requires alignment of the symbol spaces of  $M$ , and detection of duplications of reaction space. It is intractable in time for a human to perform this task repetitively, though model evolution would require it. We propose a new system involving OREMP [2], which provides a human-tractable system to do this job. This capability is available in the biological pathway environment called Cytosolve [3]. This system maintains the separateness of individual models while affecting a federated simulation with mass balance at intermittent time points. This approach requires adaptive time-stepping that must handle complex cross-model ODE stiffness problems that are currently under investigation (D.A. Nordsletten, private communication).

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### References:

- [1] M. C. Fishman and J. A. Porter, *Nature*, vol. 437, pp. 491-3, Sep 22 2005.
- [2] Umeton, *et al.*, *Proc. Int. Whshp on Ontology Repositories and Editors*, Crete, 2010, pp. 26-30.
- [3] V. A. Ayyadurai and C. F. Dewey, Jr. *Cell Mol Bioeng*, vol. 4, pp. 28-45, Mar 2011.
- [4] D. A. Nordsletten, *et al.*, *Prog Biophys Mol Biol*, vol. 104, pp. 77-88, Jan 2011.



**Figure 1. Design for a flexible and configurable cross-platform *in silico* model to accelerate drug development. Information from cross prediction is propagated back into the individual models that comprise each of the prediction steps shown.**