

Bond graphs for Biological Systems: Melbourne Group Publications

- [1] Peter J. Gawthrop and Edmund J. Crampin. Energy-based analysis of biochemical cycles using bond graphs. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Science*, 470(2171):1--25, 2014. Available at arXiv:1406.2447. [bib | DOI | arXiv]

Thermodynamic aspects of chemical reactions have a long history in the physical chemistry literature. In particular, biochemical cycles require a source of energy to function. However, although fundamental, the role of chemical potential and Gibb's free energy in the analysis of biochemical systems is often overlooked leading to models which are physically impossible. The bond graph approach was developed for modelling engineering systems, where energy generation, storage and transmission are fundamental. The method focuses on how power flows between components and how energy is stored, transmitted or dissipated within components. Based on the early ideas of network thermodynamics, we have applied this approach to biochemical systems to generate models which automatically obey the laws of thermodynamics. We illustrate the method with examples of biochemical cycles. We have found that thermodynamically compliant models of simple biochemical cycles can easily be developed using this approach. In particular, both stoichiometric information and simulation models can be developed directly from the bond graph. Furthermore, model reduction and approximation while retaining structural and thermodynamic properties is facilitated. Because the bond graph approach is also modular and scaleable, we believe that it provides a secure foundation for building thermodynamically compliant models of large biochemical networks.

- [2] Peter J. Gawthrop, Joseph Cursons, and Edmund J. Crampin. Hierarchical bond graph modelling of biochemical networks. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 471(2184):1--23, 2015. Available at arXiv:1503.01814. [bib | DOI | arXiv]

The bond graph approach to modelling biochemical networks is extended to allow hierarchical construction of complex models from simpler components. This is made possible by representing the simpler components as thermodynamically open systems exchanging mass and energy via ports. A key feature of this approach is that the resultant models are robustly thermodynamically compliant: the thermodynamic compliance is not dependent on precise numerical values of parameters. Moreover, the models are reusable owing to the well-defined interface provided by the energy ports. To extract bond graph model parameters from parameters found in the literature, general and compact formulae are developed to relate free-energy constants and equilibrium constants. The existence and uniqueness of solutions is considered in terms of fundamental properties of stoichiometric matrices. The approach is illustrated by building a hierarchical bond graph model of glycogenolysis in skeletal muscle.

- [3] P. J. Gawthrop and E. J. Crampin. Modular bond-graph modelling and analysis of biomolecular systems. *IET Systems Biology*, 10(5):187--201, October 2016. Available at arXiv:1511.06482. [bib | DOI | arXiv]

Bond graphs can be used to build thermodynamically-compliant hierarchical models of biomolecular systems. As bond graphs have been widely used to model, analyse and synthesise engineering systems, this study suggests that they can play the same rôle in the modelling, analysis and synthesis of biomolecular systems. The particular structure of bond graphs arising from biomolecular systems is established and used to elucidate the relation between thermodynamically closed and open systems. Block diagram representations of the dynamics implied by these bond graphs are used to reveal implicit feedback structures and are linearised to allow the application of control-theoretical methods. Two concepts of modularity are examined: computational modularity where physical correctness is retained and behavioural modularity where module behaviour (such as ultrasensitivity) is retained. As well as providing computational modularity, bond graphs provide a natural formulation of behavioural modularity and reveal the sources of retroactivity. A bond graph approach to reducing retroactivity, and thus inter-module interaction, is shown to require a power supply such as that provided by the $\text{ATP} \rightarrow \text{ADP} + \text{Pi}$ reaction. The mitogen-activated protein kinase cascade (Raf-MEK-ERK pathway) is used as an illustrative example.

Keywords: biology computing;bond graphs;enzymes;hierarchical systems;molecular biophysics;physiological models;thermodynamics;ATP \rightarrow ADP + Pi reaction;Michaelis-Menten kinetics;Raf-MEK-ERK pathway;behavioural modularity;biomolecular systems;block diagram representations;computational modularity;intermodule interaction;mitogen-activated protein kinase cascade;modular bond-graph modelling;retroactivity;signalling networks;thermodynamically-compliant hierarchical models

- [4] Peter J. Gawthrop. Bond-graph modelling and causal analysis of biomolecular systems. In Wolfgang Borutzky, editor, *Bond Graphs for Modelling, Control and Fault Diagnosis of Engineering Systems*, pages 587--623. Springer International Publishing, Berlin, 2017. [bib | DOI]

Bond graph modelling of the biomolecular systems of living organisms is introduced. Molecular species are represented by non-linear C components and reactions by non-linear two-port R components. As living systems are neither at thermodynamic equilibrium nor closed, open and non-equilibrium systems are considered and illustrated using examples of biomolecular systems. Open systems are modelled using chemostats: chemical species with fixed concentration. In addition to their role in ensuring that models are energetically correct, bond graphs provide a powerful and natural way of representing and analysing causality. Causality is used in this chapter to examine the properties of the junction structures of biomolecular systems and how they relate to biomolecular concepts.

- [5] Peter J. Gawthrop and Edmund J. Crampin. Energy-based analysis of biomolecular pathways. *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, 473(2202), 2017. Available at arXiv:1611.02332. [bib | DOI | arXiv]

Decomposition of biomolecular reaction networks into pathways is a powerful approach to the analysis of metabolic and signalling networks. Current approaches based on analysis of the stoichiometric matrix reveal information about steady-state mass flows (reaction rates) through the network. In this work, we show how pathway analysis of biomolecular networks can be extended using an energy-based approach to provide information about energy flows through the network. This energy-based approach is developed using the engineering-inspired bond graph methodology to represent biomolecular reaction networks. The approach is introduced using glycolysis as an exemplar; and is then applied to analyse the efficiency of free energy transduction in a biomolecular cycle model of a transporter protein [sodium-glucose transport protein 1 (SGLT1)]. The overall aim of our work is to present a framework for modelling and analysis of biomolecular reactions and processes which considers energy flows and losses as well as mass transport.

- [6] P. J. Gawthrop, I. Siekmann, T. Kameneva, S. Saha, M. R. Ibbotson, and E. J. Crampin. Bond graph modelling of chemoelectrical energy transduction. *IET Systems Biology*, 11(5):127--138, 2017. Available at arXiv:1512.00956. [bib | DOI | arXiv]

Energy-based bond graph modelling of biomolecular systems is extended to include chemoelectrical transduction thus enabling integrated thermodynamically compliant modelling of chemoelectrical systems in general and excitable membranes in particular. Our general approach is illustrated by recreating a well-known model of an excitable membrane. This model is used to investigate the energy consumed during a membrane action potential thus contributing to the current debate on the trade-off between the speed of an action potential event and energy consumption. The influx of Na⁺ is often taken as a proxy for energy consumption; in contrast, this study presents an energy-based model of action potentials. As the energy-based approach avoids the assumptions underlying the proxy approach it can be directly used to compute energy consumption in both healthy and diseased neurons. These results are illustrated by comparing the energy consumption of healthy and degenerative retinal ganglion cells using both simulated and in vitro data.

Keywords: biochemistry;bioelectric potentials;biomembrane transport;eye;molecular biophysics;neurophysiology;sodium;Na;biomolecular systems;chemoelectrical energy transduction;chemoelectrical systems;degenerative retinal ganglion cells;diseased neurons;energy consumption;energy-based bond graph modelling;excitable membranes;healthy neurons;healthy retinal ganglion cells;integrated thermodynamically compliant modelling;membrane action potential

- [7] P. J. Gawthrop. Bond graph modeling of chemiosmotic biomolecular energy transduction. *IEEE Transactions on NanoBioscience*, 16(3):177--188, April 2017. Available at arXiv:1611.04264. [bib | DOI | arXiv]

Engineering systems modeling and analysis based on the bond graph approach has been applied to biomolecular systems. In this context, the notion of a Faraday-equivalent chemical potential is introduced which allows chemical potential to be expressed in an analogous manner to electrical volts thus allowing engineering intuition to be applied to biomolecular systems. Redox reactions, and their representation by half-reactions, are key components of biological systems which involve both electrical and chemical domains. A bond graph interpretation of redox reactions is given which combines bond graphs with the Faraday-equivalent chemical potential. This approach is particularly relevant when the biomolecular system implements chemoelectrical transduction â for example chemiosmosis within the key metabolic pathway of mitochondria: oxidative phosphorylation. An alternative way of implementing computational modularity using bond graphs is introduced and used to give a physically based model of the mitochondrial electron transport chain To illustrate the overall approach, this model is analyzed using the Faraday-equivalent chemical potential approach and engineering intuition is used to guide affinity equalisation: a energy based analysis of the mitochondrial electron transport chain.

Keywords: Analytical models;Biological system modeling;Chemicals;Computational modeling;Context;Electric potential;Protons;Biological system modeling;computational systems biology;systems biology

- [8] Peter J. Gawthrop and Edmund J. Crampin. Biomolecular system energetics. In *Proceedings of the 13th International Conference on Bond Graph Modeling (ICBGM'18)*, Bordeaux, 2018. Society for Computer Simulation. Available at arXiv:1803.09231. [bib | arXiv]

Efficient energy transduction is one driver of evolution; and thus understanding biomolecular energy transduction is crucial to understanding living organisms. As an energy-orientated modelling methodology, bond graphs provide a useful approach to describing and modelling the efficiency of living systems. This paper gives some new results on the efficiency of metabolism based on bond graph models of the key metabolic processes: glycolysis.

- [9] Michael Pan, Peter J. Gawthrop, Kenneth Tran, Joseph Cursons, and Edmund J. Crampin. Bond graph modelling of the cardiac action potential: implications for drift and non-unique steady states. *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, 474(2214), 2018. Available at arXiv:1802.04548. [bib | DOI | arXiv]

Mathematical models of cardiac action potentials have become increasingly important in the study of heart disease and pharmacology, but concerns linger over their robustness during long periods of simulation, in particular due to issues such as model drift and non-unique steady states. Previous studies have linked these to violation of conservation laws, but only explored those issues with respect to charge conservation in specific models. Here, we propose a general and systematic method of identifying conservation laws hidden in models of cardiac electrophysiology by using bond graphs, and develop a bond graph model of the cardiac action potential to study long-term behaviour. Bond graphs provide an explicit energy-based framework for modelling physical systems, which makes them well suited for examining conservation within electrophysiological models. We find that the charge conservation laws derived in previous studies are examples of the more general concept of a conserved moiety. Conserved moieties explain model drift and non-unique steady states, generalizing the results from previous studies. The bond graph approach provides a rigorous method to check for drift and non-unique steady states in a wide range of cardiac action potential models, and can be extended to examine behaviours of other excitable systems.

- [10] P. Gawthrop. Computing biomolecular system steady-states. *IEEE Transactions on NanoBioscience*, 17(1):36--43, March 2018. Published online 25th December 2017. [bib | DOI]

A new approach to compute the equilibria and the steady-states of biomolecular systems modeled by bond graphs is presented. The approach is illustrated using a model of a biomolecular cycle representing a membrane transporter and a model of the mitochondrial electron transport chain.

Keywords: Biological system modeling;Chemicals;Electric potential;Kinetic theory;Mathematical model;Nanobioscience;Steady-state;Biological system modeling;computational systems biology;systems biology

- [11] P. Gawthrop and E. J. Crampin. Bond graph representation of chemical reaction networks. *IEEE Transactions on NanoBioscience*, 17(4):449--455, October 2018. Available at arXiv:1809.00449. [bib | DOI | arXiv]

The Bond Graph approach and the Chemical Reaction Network approach to modelling biomolecular systems developed independently. This paper brings together the two approaches by providing a bond graph interpretation of the chemical reaction network concept of complexes. Both closed and open systems are discussed. The method is illustrated using a simple enzyme-catalysed reaction and a trans-membrane transporter.

Keywords: Chemicals;Junctions;Substrates;Standards;Nanobioscience;Biological system modeling;Open systems

- [12] Michael Pan, Peter J. Gawthrop, Kenneth Tran, Joseph Cursons, and Edmund J. Crampin. A thermodynamic framework for modelling membrane transporters. *Journal of Theoretical Biology*, 481:10 -- 23, 2019. Available at arXiv:1806.04341. [bib | DOI | arXiv]

Membrane transporters contribute to the regulation of the internal environment of cells by translocating substrates across cell membranes. Like all physical systems, the behaviour of membrane transporters is constrained by the laws of thermodynamics. However, many mathematical models of transporters, especially those incorporated into whole-cell models, are not thermodynamically consistent, leading to unrealistic behaviour. In this paper we use a physics-based modelling framework, in which the transfer of energy is explicitly accounted for, to develop thermodynamically consistent models of transporters. We then apply this methodology to model two specific transporters: the cardiac sarcoplasmic/endoplasmic Ca²⁺ ATPase (SERCA) and the cardiac Na⁺/K⁺ ATPase.

Keywords: Bond graph, Biochemistry, Chemical reaction network, Biomedical engineering, Systems biology

- [13] Peter J. Gawthrop, Peter Cudmore, and Edmund J. Crampin. Physically-plausible modelling of biomolecular systems: A simplified, energy-based model of the mitochondrial electron transport chain. *Journal of Theoretical Biology*, 493:110223, 2020. [bib | DOI]

Advances in systems biology and whole-cell modelling demand increasingly comprehensive mathematical models of cellular biochemistry. Such models require the development of simplified representations of specific processes which capture essential biophysical features but without unnecessarily complexity. Recently there has been renewed interest in thermodynamically-based modelling of cellular processes. Here we present an approach to developing of simplified yet thermodynamically consistent (hence physically plausible) models which can readily be incorporated into large scale biochemical descriptions but which do not require full mechanistic detail of the underlying processes. We illustrate the approach through development of a simplified, physically plausible model of the mitochondrial electron transport chain and show that the simplified model behaves like the full system.

Keywords: Systems biology, Thermodynamical modelling, Bond graph, Computational biology

- [14] Michael Pan, Peter J. Gawthrop, Joseph Cursons, Kenneth Tran, and Edmund J. Crampin. The cardiac Na⁺/K⁺ ATPase: An updated, thermodynamically consistent model. *Physiome*, 8 2020. [bib | DOI]

The Na⁺/K⁺ATPase is an essential component of cardiac electrophysiology, maintaining physiological Na⁺ and K⁺ concentrations over successive heart beats. Terkildsen et al. (2007) developed a model of the ventricular myocyte Na⁺/K⁺ ATPase to study extracellular potassium accumulation during ischaemia, demonstrating the ability to recapitulate a wide range of experimental data, but unfortunately there was no archived code associated with the original manuscript. Here we detail an updated version of the model and provide CellML and MATLAB code to ensure reproducibility and reusability. We note some errors within the original formulation which have been corrected to ensure that the model is thermodynamically consistent, and although this required some reparameterisation, the resulting model still provides a good fit to experimental measurements that demonstrate the dependence of Na⁺/K⁺ ATPase pumping rate upon membrane voltage and metabolite concentrations. To demonstrate thermodynamic consistency we also developed a bond graph version of the model. We hope that these models will be useful for community efforts to assemble a whole-cell cardiomyocyte model which facilitates the investigation of cellular energetics.

- [15] Peter J. Gawthrop and Michael Pan. Network thermodynamical modeling of bioelectrical systems: A bond graph approach. *Bioelectricity*, 3(1):3--13, Mar 2021. Published Online: 18 Dec 2020. [bib | DOI]

Interactions among biomolecules, electrons, and protons are essential to many fundamental processes sustaining life. It is therefore of interest to build mathematical models of these bioelectrical processes not only to enhance understanding but also to enable computer models to complement in vitro and in vivo experiments. Such models can never be entirely accurate; it is nevertheless important that the models are compatible with physical principles. Network Thermodynamics, as implemented with bond graphs, provide one approach to creating physically compatible mathematical models of bioelectrical systems. This is illustrated using simple models of ion channels, redox reactions, proton pumps, and electrogenic membrane transporters thus demonstrating that the approach can be used to build mathematical and computer models of a wide range of bioelectrical systems.

- [16] Peter J. Gawthrop, Michael Pan, and Edmund J. Crampin. Modular dynamic biomolecular modelling with bond graphs: the unification of stoichiometry, thermodynamics, kinetics and data. *Journal of The Royal Society Interface*, 18(181):20210478, 2021. [bib | DOI]

Renewed interest in dynamic simulation models of biomolecular systems has arisen from advances in genome-wide measurement and applications of such models in biotechnology and synthetic biology. In particular, genome-scale models of cellular metabolism beyond the steady state are required in order to represent transient and dynamic regulatory properties of the system. Development of such whole-cell models requires new modelling approaches. Here, we propose the energy-based bond graph methodology, which integrates stoichiometric models with thermodynamic principles and kinetic modelling. We demonstrate how the bond graph approach intrinsically enforces thermodynamic constraints, provides a modular approach to modelling, and gives a basis for estimation of model parameters leading to dynamic models of biomolecular systems. The approach is illustrated using a well-established stoichiometric model of *Escherichia coli* and published experimental data.

- [17] Peter Cudmore, Michael Pan, Peter J. Gawthrop, and Edmund J. Crampin. Analysing and simulating energy-based models in biology using BondGraphTools. *The European Physical Journal E*, 44(12):148, Dec 2021. [bib | DOI]

Like all physical systems, biological systems are constrained by the laws of physics. However, mathematical models of biochemistry frequently neglect the conservation of energy, leading to unrealistic behaviour. Energy-based models that are consistent with conservation of mass, charge and energy have the potential to aid the understanding of complex interactions between biological components, and are becoming easier to develop with recent advances in experimental measurements and databases. In this paper, we motivate the use of bond graphs (a modelling tool from engineering) for energy-based modelling and introduce, BondGraphTools, a Python library for constructing and analysing bond graph models. We use examples from biochemistry to illustrate how BondGraphTools can be used to automate model construction in systems biology while maintaining consistency with the laws of physics.

- [18] Michael Pan, Peter J. Gawthrop, Joseph Cursons, and Edmund J. Crampin. Modular assembly of dynamic models in systems biology. *PLOS Computational Biology*, 17(10):1--27, 10 2021. [bib | DOI]

It is widely acknowledged that the construction of large-scale dynamic models in systems biology requires complex modelling problems to be broken up into more manageable pieces. To this end, both modelling and software frameworks are required to enable modular modelling. While there has been consistent progress in the development of software tools to enhance model reusability, there has been a relative lack of consideration for how underlying biophysical principles can be applied to this space. Bond graphs combine the aspects of both modularity and physics-based modelling. In this paper, we argue that bond graphs are compatible with recent developments in modularity and abstraction in systems biology, and are thus a desirable framework for constructing large-scale models. We use two examples to illustrate the utility of bond graphs in this context: a model of a mitogen-activated protein kinase (MAPK) cascade to illustrate the reusability of modules and a model of glycolysis to illustrate the ability to modify the model granularity.

- [19] P. J. Gawthrop. Energy-based modeling of the feedback control of biomolecular systems with cyclic flow modulation. *IEEE Transactions on NanoBioscience*, 20(2):183--192, April 2021. [bib | DOI]

Energy-based modelling brings engineering insight to the understanding of biomolecular systems. It is shown how well-established control engineering concepts, such as loop-gain, arise from energy feedback loops and are therefore amenable to control engineering insight. In particular, a novel method is introduced to allow the transfer function based approach of classical linear control to be utilised in the analysis of feedback systems modelled by network thermodynamics and thus amalgamate energy-based modelling with control systems analysis. The approach is illustrated using a class of metabolic cycles with activation and inhibition leading to the concept of Cyclic Flow Modulation.

Keywords: Biological system modeling;Junctions;Transfer functions;Thermodynamics;Mathematical model;Feedback loop;Analytical models;Biological system modeling;computational systems biology;systems biology;negative feedback

- [20] Niloofar Shahidi, Michael Pan, Soroush Safaei, Kenneth Tran, Edmund J. Crampin, and David P. Nickerson. Hierarchical semantic composition of biosimulation models using bond graphs. *PLOS Computational Biology*, 17(5):e1008859, May 2021. [bib | DOI]

Author summary Biological and physiological systems usually involve multiple underlying processes, mechanisms, structures, and phenomena, referred to here as sub-systems. Modelling the whole system every time from scratch requires a huge amount of effort. An alternative is to model each sub-system in a modular fashion, i.e., containing meaningful interfaces for connecting to other modules. Such modules are readily combined to produce a whole-system model. For the combined model to be consistent, modules must be described using the same modelling scheme. One way to achieve this is to use energy-based models that are consistent with the conservation laws of physics. Here, we present an approach that achieves this using bond graphs, which allows modules to be combined faster and more efficiently. First, physically plausible modules are generated using a small number of template modules. Then a meaningful interface is added to each module to automate connection. This approach is illustrated by applying this method to an existing model of the circulatory system and verifying the results against the reference model.

- [21] Peter J. Gawthrop and Michael Pan. Network thermodynamics of biological systems: A bond graph approach. *Mathematical Biosciences*, 352:108899, 2022. [bib | DOI]

Edmund Crampin (1973-2021) was at the forefront of Systems Biology research and his work will influence the field for years to come. This paper brings together and summarises the seminal work of his group in applying energy-based bond graph methods to biological systems. In particular, this paper: (a) motivates the need to consider energy in modelling biology; (b) introduces bond graphs as a methodology for achieving this; (c) describes extensions to modelling electrochemical transduction; (d) outlines how bond graph models can be constructed in a modular manner and (e) describes stoichiometric approaches to deriving fundamental properties of reaction networks. These concepts are illustrated using a new bond graph model of photosynthesis in chloroplasts.

Keywords: Systems biology, Bond graph, Energy-based, Photosynthesis, Electrochemical transduction

- [22] Peter J. Gawthrop and Michael Pan. Energy-based advection modelling using bond graphs. *Journal of The Royal Society Interface*, 19(195):20220492, 2022. [bib | DOI]

Advection, the transport of a substance by the flow of a fluid, is a key process in biological systems. The energy-based bond graph approach to modelling chemical transformation within reaction networks is extended to include transport and thus advection. The approach is illustrated using a simple model of advection via circulating flow and by a simple pharmacokinetic model of anaesthetic gas uptake. This extension provides a physically consistent framework for linking advective flows with the fluxes associated with chemical reactions within the context of physiological systems in general and the human physiome in particular.

- [23] Niloofar Shahidi, Michael Pan, Kenneth Tran, Edmund J. Crampin, and David P. Nickerson. Sbm1 to bond graphs: From conversion to composition. *Mathematical Biosciences*, 352:108901, 2022. [bib | DOI]

The Systems Biology Markup Language (SBML) is a popular software-independent XML-based format for describing models of biological phenomena. The BioModels Database is the largest online repository of SBML models. Several tools and platforms are available to support the reuse and composition of SBML models. However, these tools do not explicitly assess whether models are physically plausible or thermodynamically consistent. This often leads to ill-posed models that are physically impossible, impeding the development of realistic complex models in biology. Here, we present a framework that can automatically convert SBML models into bond graphs, which imposes energy conservation laws on these models. The new bond graph models are easily mergeable, resulting in physically plausible coupled models. We illustrate this by automatically converting and coupling a model of pyruvate distribution to a model of the pentose phosphate pathway.

Keywords: SBML, BioModels, Bond graphs, Automatic conversion, Glycolysis, Pentose phosphate pathway

- [24] Niloofar Shahidi, Michael Pan, Kenneth Tran, Edmund J. Crampin, and David P. Nickerson. A semantics, energy-based approach to automate biomodel composition. *PLOS ONE*, 17(6):1--36, 06 2022. [bib | DOI]

Hierarchical modelling is essential to achieving complex, large-scale models. However, not all modelling schemes support hierarchical composition, and correctly mapping points of connection between models requires comprehensive knowledge of each model's components and assumptions. To address these challenges in integrating biosimulation models, we propose an approach to automatically and confidently compose biosimulation models. The approach uses bond graphs to combine aspects of physical and thermodynamics-based modelling with biological semantics. We improved on existing approaches by using semantic annotations to automate the recognition of common components. The approach is illustrated by coupling a model of the Ras-MAPK cascade to a model of the upstream activation of EGFR. Through this methodology, we aim to assist researchers and modellers in readily having access to more comprehensive biological systems models.

- [25] Vijay Rajagopal, Senthil Arumugam, Peter J. Hunter, Afshin Khadangi, Joshua Chung, and Michael Pan. The cell physiome: What do we need in a computational physiology framework for predicting single-cell biology? *Annual Review of Biomedical Data Science*, 5(1):341--366, 2022. PMID: 35576556. [bib | DOI]

Modern biology and biomedicine are undergoing a big data explosion, needing advanced computational algorithms to extract mechanistic insights on the physiological state of living cells. We present the motivation for the Cell Physiome Project: a framework and approach for creating, sharing, and using biophysics-based computational models of single-cell physiology. Using examples in calcium signaling, bioenergetics, and endosomal trafficking, we highlight the need for spatially detailed, biophysics-based computational models to uncover new mechanisms underlying cell biology. We review progress and challenges to date toward creating cell physiome models. We then introduce bond graphs as an efficient way to create cell physiome models that integrate chemical, mechanical, electromagnetic, and thermal processes while maintaining mass and energy balance. Bond graphs enhance modularization and reusability of computational models of cells at scale. We conclude with a look forward at steps that will help fully realize this exciting new field of mechanistic biomedical data science.