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3

# *In silico* modelling of physiologic systems

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*In silico* modelling, in which computer models are developed to model a pharmacologic or physiologic process, is a logical extension of controlled *in vitro* experimentation. It is the natural result of the explosive increase in computing power available to the research scientist at continually decreasing cost.

*In silico* modelling combines the advantages of both *in vivo* and *in vitro* experimentation, without subjecting itself to the ethical considerations and lack of control associated with *in vivo* experiments. Unlike *in vitro* experiments, which exist in isolation, *in silico* models allow the researcher to include a virtually unlimited array of parameters, which render the results more applicable to the organism as a whole.

*In silico* modelling is best known for its extensive use in pharmacokinetic experimentation, the best-known example of which is the development of the three-compartment model. In addition, complex *in silico* models have been applied to pathophysiological problems to provide information which cannot be obtained practically or ethically by traditional clinical research methods. These experiments have led to the development of significant insights in subject matters ranging from pure physiology to congenital heart surgery, obstetric anaesthesia airway management, mechanical ventilation and cardiopulmonary bypass/ventricular support devices.

The utility of these models is based on both the validity of the model framework as well as the corresponding assumptions. *In vivo* experimentation has validated some, but not all of the *in silico* strategies employed. We present a review illustrating by example how *in silico* modelling has been applied to a number of cardio-respiratory problems in states of health and disease, the

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purpose of which is to give the reader a sense of the complexity and assumptions which underlie this diverse and underappreciated research strategy, as well as an introduction to a research strategy that will likely continue to grow in importance.



## Introduction

Classically, scientific research has been divided into two types – *in vivo* ('within the living') and *in vitro* ('within glass'). The development of *in vitro* techniques was a response to several considerations, including the ethics of experimenting on live subjects, the cost (time and resources) associated with experimenting on live subjects and the inability to control conditions properly.

*In vitro* experiments can be more tightly controlled than *in vivo* experiments, and can generally be undertaken more quickly and with fewer resources. However, a major criticism of *in vitro* experiments is that they do not accurately represent the organism as a whole. Modern biomedical literature is littered with tales of therapeutic agents that exhibited great promise in the controlled setting of the basic science laboratory, only to fail miserably when applied to animal or human subjects.

The invention of the microprocessor and subsequent development of the personal computer has led to numerous scientific advances. One of the most exciting, and least developed, is in the field of *in silico* ('in silicon') research. *In silico* research, in which mathematical models of a physiologic or pharmacologic system are developed and tested on a computer, are a hybrid of *in vivo* and *in vitro* techniques.

Like *in vivo* techniques, *in silico* experiments are designed to mimic the behaviour of organisms in their entirety. However, like *in vitro* experiments, they do not require actual experimentation on animal subjects. Furthermore, conditions can be controlled with exquisite detail, because the investigator defines them as part of the model employed.

*In silico* techniques, thus, offer the clinician-scientist the opportunity to answer questions that, for a variety of reasons, could not otherwise be easily addressed. Most readers are familiar with the major advances in pharmacokinetics that have resulted from the development and application of sophisticated *in silico* techniques, most notably the addition of the third ('effect site') compartment to pharmacokinetic models and the subsequent improvement in their predictive abilities (for an outstanding introduction, see the work of Shafer).[1] These techniques need not be limited to the field of pharmacology, however.

The purpose of this review is to introduce the reader to a few of the arenas of *in silico* experimentation, to describe the physiologic insights that have been gained thus far and to provide a brief introduction into the techniques themselves. Because of the varied nature of the models employed by different investigators, it is not possible to describe the technical details of each approach with sufficient clarity to allow for reproduction. Our goal is not to 'recreate' these models but to direct the reader towards this groundbreaking work.

## Physiologic experimentation

### *Ventricular interdependence*

Santamore and Burkhoff used an electrical circuit-based analogue of the cardiovascular system to study the haemodynamic effects of left (LV) and right ventricular (RV) interaction. In this haemodynamic model, both the systemic and pulmonic vascular systems were modelled using a five-element system – three resistors, which represented ventricular outflow impedance, resistance to arterial flow and resistance to venous return, respectively, and two capacitors, which represented arterial and venous capacitance.

Ventricular contraction was modelled using time-varying elastance ('stiffness', abbreviated $E$) equations (in which $\Delta V/\Delta P$ changes with time) as well as incorporation of diodes to restrict regurgitant valvular flow.[2] For the purposes of this experiment, maximal elastance ($E_{max}$) was considered to be