in gene expression can affect evolution and predicted that the level of evolved cell-to-cell variability in the population depends on the associated fitness costs and benefits of gene expression in a specific environment. An exact algorithm for fast stochastic simulations of evolutionary dynamics was developed by Mather et al., [150], which provides a significant speedup when the population size is large and mutation rates are much smaller than the birth and death rates.

5. Discussion

We have covered some of the common mathematical and computational methods for investigating cell population dynamics. To balance comprehensiveness with length of the review, several modeling approaches were omitted out of necessity, not due to lack of importance. For instance, spatial models can be critical for predicting the behavior and fate of cell populations. Spatial models often involve compartmentalized ordinary differential equations [35], stochastic differential equations of motion [38], partial differential equations and various computational approaches that have been derived from cellular automata [45]. These models have been used to describe a wide range of phenomena, from T-cell population dynamics [35], to tumor growth, cancer metastasis, and chemotherapy resistance [151]. For cases where only "population snapshots" are available, which provide single-cell measurements at every time point (such as with flow cytometric analysis) but do not provide single-cell time series data (because the cells are discarded after each measurement), Bayesian approaches can be used to identify models of heterogeneous cell populations [32]. In a complementary fashion, there are also methods available to deconvolve cell population dynamics from single-cell data (e.g., [152]).

Model parameterization is as important as the structure of the model. Much effort has been devoted to developing optimization techniques, which involve scanning the parameter space to minimize a cost function (i.e., minimize the error between the output of the model and the experimental data) [153]. Common optimization techniques include linear and nonlinear least-squares fitting [154], simulated annealing [155], genetic algorithms [156], and evolutionary computation [157, 158]. The problems with optimization methods are that they can be computationally expensive and may not perform well on noisy data sets [153]. Bayesian methods can infer whole probabil-

ity distributions of the parameters (rather than just a point estimate) when the data includes measurement noise and/or intrinsic noise. The challenge here is that analytic approaches are generally intractable and numerical solutions are challenging due to the need to solve high-dimensional integration problems. Maximum likelihood estimation has also been widely applied [153, 159, 160]. The appropriate parameter inference method depends on the modeling framework, and moving between frameworks (e.g., deterministic to stochastic) may involve recalculating the parameters. For example, parameters for zero order (e.g., $\varnothing \xrightarrow{ko} A$) and first order reactions (e.g., $A \xrightarrow{k1} B$) are the same in deterministic and stochastic frameworks, but second order reactions (e.g., $A + B \xrightarrow{k2} C$) require the reaction parameter to be rescaled by the cell volume V for the stochastic framework ($k2' = k2/N_A V$, where N_A is Avogadro's number). Since biological parameters often change with experimental conditions, a given parameter set will often have to be rescaled or refit to the data. Using parameters obtained in different studies can be useful to approximate the lower and upper bounds of the parameter values, though caution must be used to ensure that the best-fit parameter set corresponds to the biological system under investigation. A biologically realistic parameter set allows a model to be invalidated if it cannot fit or predict the experimental data using these parameters, and in turn model invalidation techniques can aid in finding suitable parameters or indicate if the model structure should be refined [161]. This approach tells us if a model is "good" (i.e., the model can produce behavior that shares the characteristics of the experimental data), not if it is the best model. To select the "best" model, one can use likelihood based approaches or Bayesian methods (see [24]). Likelihood methods involve determining the maximum value of a likelihood function for the competing models, obtaining the likelihood ratio, and calculating p-values under an appropriate chi-squared distribution [162]. This approach works well for a pair of nested models (one model is a special case of the other) and informs us if the improvement from using a more complex model is significant or not. When non-nested or a larger set of models are being considered, methods from information theory are appropriate. Akaike's Information Criterion (AIC) is one such method used to compare a set of models to the observed data. The improved AIC differences and Akaike weights tell us which model is correct, conditional

on the data and the set of models being considered. Bayesian Information Criterion (BIC), which unlike the AIC is unbiased for large sample sizes, can be used to estimate the marginal probability of the data given the models [162]. Bayesian methods are becoming increasingly common in computational systems biology [163] and synthetic biology [164]. The main objective here for parameter inference is determining the posterior distribution, whereas for model comparison the marginal likelihood is the key objective [24].

The field of computational biology is presently lacking comprehensive "user-friendly", customizable, multiscale, computationally efficient cell population simulators, though many of these individual components are available in different software packages. CellPD, a user-friendly open source software, was developed for experimental biologists (without specialized training in computational or mathematical modeling) to automatically quantify key parameters of cell phenotypes based on fits of various mathematical cell population dynamics models to the experimental data [34]. One limitation of CellPD is that it does not support user-defined mathematical models without modifying the source code (for Python source code and executable files see ref. [165]). As mathematical modeling gained traction in biology, simulators with graphical user interfaces (GUIs) were developed to aid biologists [38]. One example is CellSys, a modular software tool developed for off-lattice simulation of growth and organization processes in multi-cellular systems in 2D and 3D [38]. To try and offset the major performance bottleneck (solving the stochastic equations of motion for each cell), the core algorithms in CellSys are parallelized using OpenMP (openmp.org), as in the asynchronous PDA. The Open Systems Pharmacology Suite is an excellent example of a software platform for multiscale modeling and simulation of whole-body physiology, disease biology, and molecular reactions networks, which facilitates efficient model development, simulation and model analysis across multiple physiological scales [166]. This software platform combines GUI-based tools (PK-Sim and MoBi [167]) with interfaces to computing environments (R [168] and Matlab [169]) for solving ordinary differential and delay differential equations. Another example is the Glazier-Graner-Hogeweg based CompuCell3D simulation environment, though Python scripting or C++ coding is required to develop modules for implementing customized or more complex models [38].

Future directions in the field involve extending existing software or creating new platforms that biologists can easily use to formulate and simulate spatial and stochastic models of cell population dynamics. The backend of such a simulator could take advantage of distributed- or shared-memory architectures [52], as well as high performance graphical processing units [170]. Machine-learning approaches are another promising direction to take advantage of increasingly large experimental data sets to build multiscale biological models [171], and to bridge the gap between detailed descriptions of intracellular molecular events [124, 125] and population dynamics. Though much progress has been made by studying single or isolated pairs of populations, true multiscale population models will one day have to account for ecological dynamics that result from interactions between a diverse set of populations [172–175], as well as intra-population dynamics in fluctuating or spatially structured environments.

The utility of quantitative models is to gain insight into living systems and make experimentally verifiable predictions. Due to the multiscale nature and combinatorial complexity of biological systems, it is difficult to develop general models that always apply. Until we gain a better understanding of the systems we are modeling, and computational resources and processing times become more ideal, we will be constrained to make approximate and somewhat *ad-hoc* models. Nevertheless, by testing various models and their ability to predict the experimental data, we can rigorously verify hypotheses about biological phenomena by comparing model predictions to experiments, and in an iterative cycle, improve our models based on the data. These models will continue to serve as a "microscope", allowing us to peer deeper into nature than experimental methods at the time allow.

Acknowledgments

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