Modern medical oncology has been evolving continuously since the mid-twentieth century based on two foundations. The discovery of agents that adversely affect the growth and viability of cancer cells was the primary motivating event, but the second is the development of a set of principles that guide their most successful application [1]. The analogy to antibiotic therapy is apt (although unfortunately too facile). Antibiotics alone would be useless without knowledge of the appropriate choice of drug or combination of drugs, proper doses and routes of administration, optimal intervals between doses, and the necessary duration of therapy. Anticancer drugs often have marked toxicities and such modest effects in comparison to antibiotics in their respective tasks, it is therefore even more important to have well-developed principles for the chemotherapy of cancer than for the chemotherapy of infections. In addition, few cancers are uniformly sensitive to any one drug. In the aggregate, reliance on the development of antibiotics to guide chemotherapy use and study, while tempting, would be unfortunate and a disease-specific approach is needed for cancer treatment.

These considerations have motivated the development and refinement of concepts of drug administration over the past decades. Examples of these developments include the use of combinations of drugs at effective doses – chosen to avoid overlapping toxicities while minimizing cross-resistance – applied beyond the achievement of clinical complete remission to treat subclinical residual disease. With these basic principles applied, cure has been obtained for many cases of several different types of cancer. Such curable cancers have the common property of being particularly sensitive to anticancer drugs and, in some cases, to very specific targeted therapies. Importantly, the principles informing the development of curative regimens are possibly even more critical in the successful treatment of less sensitive tumor types. This chapter will consider the modeling of these principles with regard to the common settings of reduced, partial, or mutable drug sensitivity and will focus on two specific concepts: sequential therapy and dose density, both of which have proven effective in recent clinical trials in early breast cancer.

Sequential therapy and dose density are both products of the modeling techniques based on tumor growth kinetics as well as phenomenological observations. These phenomenological models are important given their proven value in planning successful drug therapy. Even in this era of our rapidly evolving understanding of molecular biology, phenomenological models will serve a continued purpose because they can guide the search for the biochemical and biophysical etiologies of
cancerous and normal growth. Phenomenological models also serve as a critical translational connection between pure molecular models and quantitative clinical or laboratory observations. In other areas of quantitative science research, including mechanics, fluidics, optics, and electronics among many, the mathematical definition of a phenomenon is required for its elucidation and eventual control. In the best of circumstances there is a feedback loop between the model and scientific observations such that the mathematical model is continuously refined follow their testing against observations. The end result is an even more accurate model. Oncology has to some extent followed this paradigm, but can do so to a greater extent, and this should lead to improvements in cancer prevention, diagnosis, and prognostication in addition to therapy.

1.2 The Skipper-Schabel Model and its Relevance

As a specialty and a science, medical oncology has focused from its earliest years on in vivo rather than just in vitro experimental models of cancer growth and response [2]. As opposed to the antibiotic treatment of bacteria, in which the killing of cells in vitro is an excellent predictor of clinical benefit, cancer chemotherapy involves more intricate phenomena and, as discussed earlier, more heterogeneous patterns of sensitivity and resistance. This may be a consequence of the presumed polyclonal nature of neoplastic growths plus the myriad of host reactive cells, including elements of the immune system, supporting stroma, including blood vessels, noncellular structural elements, and anatomic derangements, that are only just now beginning to be explored and addressed therapeutically for individual patients and tumors. Our historic, but still important reliance on classifications based solely on histologic appearance may obscure potentially more important biological underpinnings for neoplastic transformation and growth. This could also explain some of the heterogeneity among tumors of the same type in different patients, since the biology of cancer may transcend individual histologic tumor types. Given the inadequacy of our theoretical and computational knowledge to handle such complexity, it remains advantageous to study biologically realistic experimental models in the expectation that they will be accurately predictive of clinical events.

One of the most influential of these models is the murine leukemia L1210 pioneered by Howard Skipper, Frank Schabel and colleagues with the support of the United States National Cancer Institute (NCI) [3]. This model was the premier focus of experimental oncology and remains critical in the design of clinical trials and the routine practice of oncology even though it has now been supplanted by models made more useful by virtue of their defined genetic background. These newer models allow us to dissect molecular events in carcinogenesis, growth regulation, and apoptosis. In contrast, L1210 was most useful because of its reproducible growth characteristics, predictable impact on mouse survival, and sensitivity to drugs that affect human cancer. In particular, L1210 has the ability to spontaneously generate drug-resistant cells, and this makes it appealing as a mimic of the heterogeneity in drug sensitivity typical of most clinical neoplasms. Building on this model,