# Integration of experimental and computational approaches to sprouting angiogenesis

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**Purpose of review**
We summarize recent experimental and computational studies that investigate molecular and cellular mechanisms of sprouting angiogenesis. We discuss how experimental tools have unveiled new opportunities for computational modeling by providing detailed phenomenological descriptions and conceptual models of cell-level behaviors underpinned by high-quality molecular data. Using recent examples, we show how new understanding results from bridging computational and experimental approaches.

**Recent findings**
Experimental data extends beyond the tip cell vs. stalk cell paradigm, and involves numerous molecular inputs such as vascular endothelial growth factor and Notch. This data is being used to generate and validate computational models, which can then be used to predict the results of hypothetical experiments that are difficult to perform in the laboratory, and to generate new hypotheses that account for system-wide interactions. As a result of this integration, descriptions of critical gradients of growth factor–receptor complexes have been generated, and new modulators of cell behavior have been described.

**Summary**
We suggest that the recent emphasis on the different stages of sprouting angiogenesis, and integration of experimental and computational approaches, should provide a way to manage the complexity of this process and help identify new regulatory paradigms and therapeutic targets.

**Keywords**
computational models, experimental models, sprouting angiogenesis, stages of angiogenesis

## INTRODUCTION

Blood vessel formation is critical to the development of all vertebrates, and co-option or dysfunction of blood vessels in diseases such as atherosclerosis and cancer is a major cause of mortality in humans. Thus, the molecular and cellular mechanisms that contribute to formation of a vascular network are potential therapeutic targets, and our understanding of these regulatory inputs has increased exponentially in the last several years. Indeed, we now have clinically approved therapies (e.g. Lucentis; Genentech, USA) that are widely prescribed in certain disease settings, such as diabetic retinopathy, to effectively modulate key molecular signals, such as the vascular endothelial growth factor (VEGF) signaling pathway. We understand that differential responses to inputs by the endothelial cells that comprise the nascent vessels, so that some cells migrate, whereas others divide, is important for the expansion of blood vessel networks via sprouting angiogenesis. We know many of the molecular pathways that contribute information for proper vessel sprouting, and we know that some of them, such as VEGF and Notch, integrate with each other to establish endothelial heterogeneity and appropriate responses.

We have also come to realize that blood vessel sprouting is a complex process, and a complete understanding of its regulation will require knowledge of which inputs are critical, and when in time

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