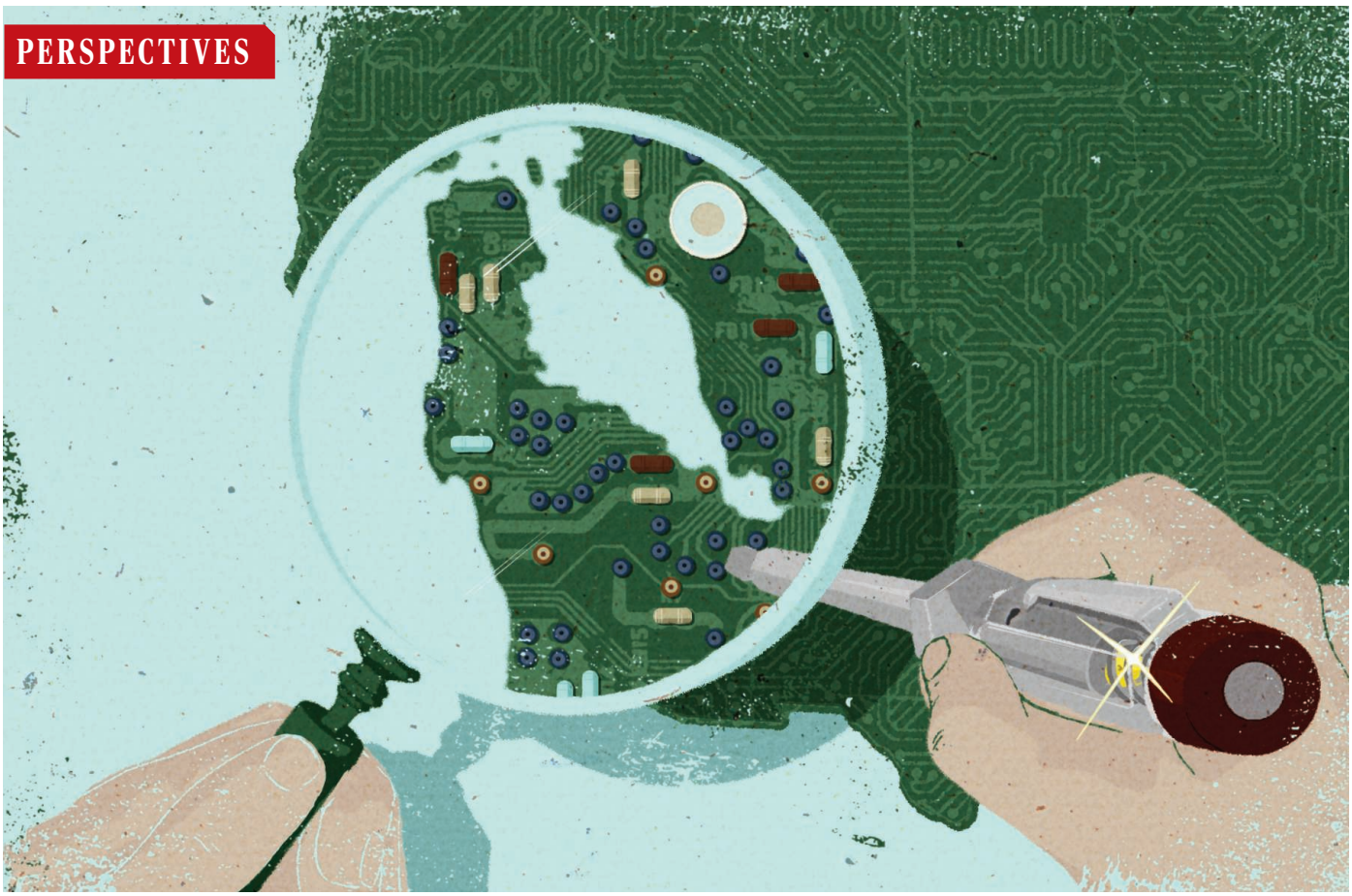
# INSIGHTS

Secondary response to infection *p. 609*

Surface control of nanoparticle properties *p. 615*

PERSPECTIVES



INNOVATION ECONOMICS

# *Where is Silicon Valley?*

## Forecasting and mapping entrepreneurial quality

*By* **Jorge Guzman**[1] *and* **Scott Stern**[1,2*]

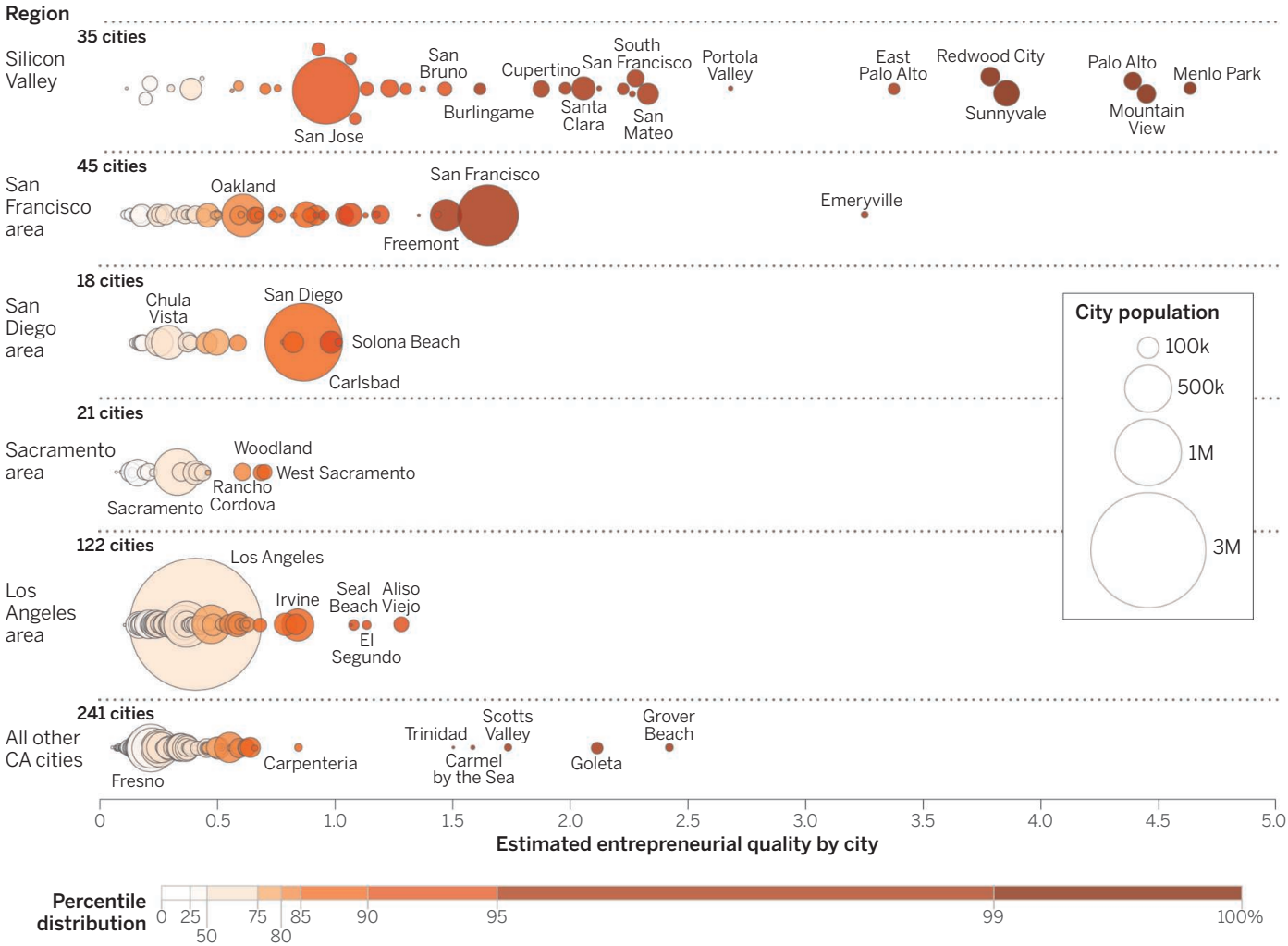
Although economists, politicians, and business leaders have long emphasized the importance of entrepreneurship (*1*, *2*), defining and characterizing entrepreneurship has been elusive (*3*, *4*). Researchers have been unable to systematically connect the type of high-impact entrepreneurship found in regions such as Silicon Valley with the overall incidence of entrepreneurship in the population (*5*–*7*). This has important implications: Researchers arrive at alternative conclusions about roles and patterns of entrepreneurship (*8*–*10*), and policy-makers are given conflicting recommendations about whether or how to promote entrepreneurship for economic and social progress (*11*, *12*).

To break this impasse, we introduce a new method for studying the founding and growth of entrepreneurial ventures. Whereas most prior studies have focused on the quantity of entrepreneurial ventures (e.g., the number of new businesses per capita in a given region), we focus on characterizing their quality. Rather than assume that all ventures have an equal ex ante probability of success, our method allows us to estimate the probability of growth based on information publicly available at or near the time of founding.

**POLICY**

We implement our approach using for-profit business registrations in California from 2001 to 2011 (*13*), combined with data from the U.S. Patent and Trademark Office and SDC Platinum [details on data and methods are in the supplementary materials (SM)]. We estimate outcomes on the basis of a small number of start-up characteristics: (i) firm name characteristics, including whether the firm name is eponymous [named after

## California quality is all over the map




**Estimating entrepreneurial quality by city.** Each bubble represents a city. Bubble size reflects city population. Bubble color varies according to quality scale at bottom of figure. Each row represents distinct geographic region. See SM.

the founder (*14*)], is short or long, is associated with local business activity or regionally traded clusters (e.g., dry cleaning versus manufactured goods), or is associated with a set of high-technology industry clusters (*15*, *16*); (ii) how the firm is registered, including whether it is a corporation [rather than partnership or limited liability company (LLC)] and whether it is incorporated in Delaware (*17*); and (iii) whether the firm establishes control over formal intellectual property (IP) rights within 1 year of registration (*18*).

To ensure that our estimate reflects the quality of start-ups in a location rather than assuming that start-ups from a given location are associated with a given level of quality, we exclude location-specific measures from the set of observable start-up characteristics.

We estimate entrepreneurial quality as the probability of achieving a meaningful growth outcome—defined as an initial public offering (IPO) or an acquisition (*19*) within 6 years of founding—as a function of these start-up characteristics. This predictive, location-agnostic algorithm can then be used to independently characterize the entrepreneurial quality of firms and locations.

**ESTIMATING ENTREPRENEURIAL QUALITY.** We estimate entrepreneurial quality through a logit model with a randomly selected sample of 70% of all firms registered in 2001–2006 (keeping the other 30% as a test sample). Our model incorporates business registration and IP factors in a single regression, with all coefficients significant at the 5% level (*20*) (table S1). When we look at firm name characteristics, eponymous firms are more than 70% less likely to grow than noneponymous firms, whereas firms with short names are 50% more likely to grow than firms with long names, and firms that include words associated with high-technology clusters are 92% more likely to grow than others. Looking at legal form and IP, corporations are >6 times more likely to grow than noncorporations, and firms with trademarks are >5 times more likely to grow than nontrademarked firms. Patenting and Delaware jurisdiction play an outsized role: Each alone is associated with a >25 times increase in the probability of growth relative to not being present. When both are present at the same time, there is nearly a 200 times increase in the probability of growth.

As a validation test, we estimate entrepreneurial quality for the test sample withheld from the original regression and so

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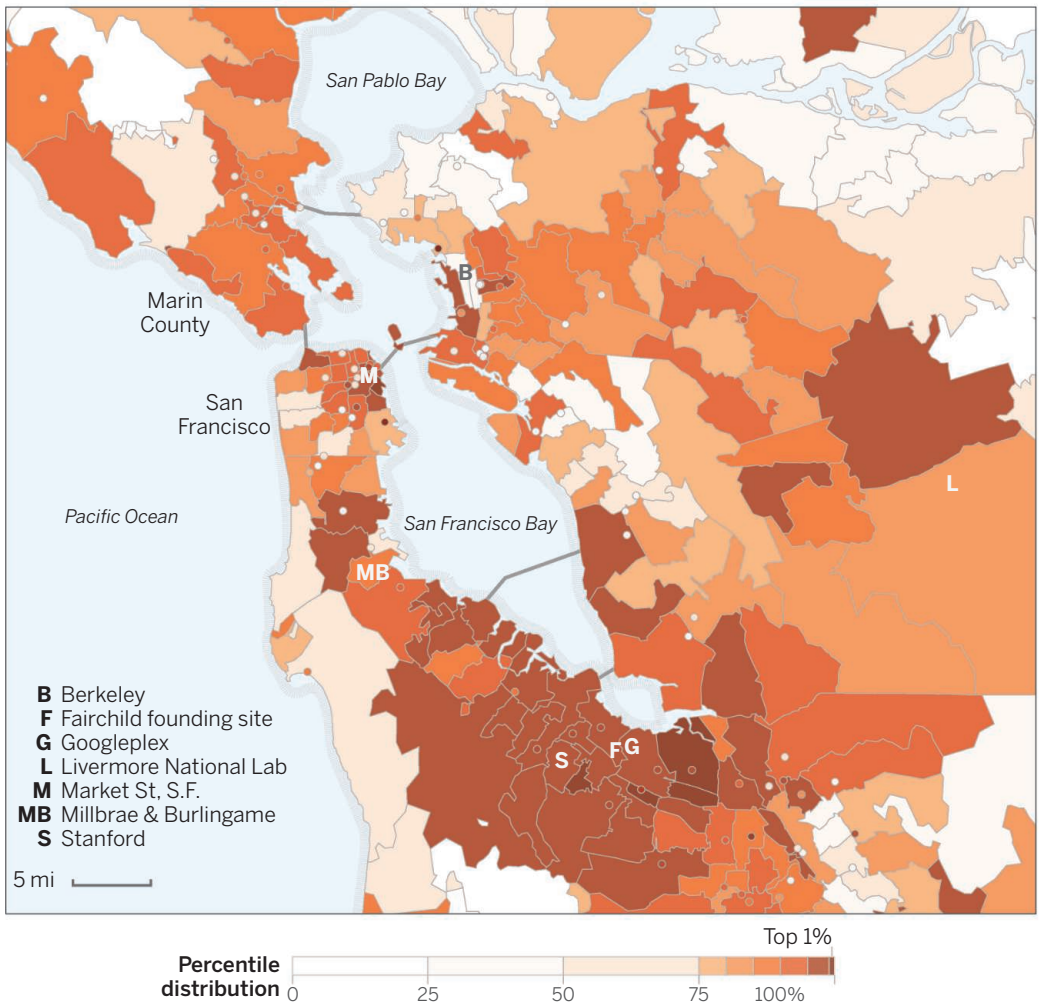
compare our predictions of entrepreneurial quality to the actual outcome distribution. Our estimate of entrepreneurial quality is strongly related to out-of-sample outcomes: 76% of all growth outcomes in the test sample are within the top 5% of the distribution of estimated entrepreneurial quality, with 56% drawn from the top 1% of that distribution (fig. S1). Highlighting the extreme uncertainty associated with entrepreneurship, growth is still rare: Even within the top 1% of estimated entrepreneurial quality, the average firm has only a 5% chance of realizing a growth outcome. This is consistent with recent findings that start-up growth is skewed relative to overall firm growth—Gibrat's law (*21*).

**MAPPING ENTREPRENEURSHIP.** The centerpiece of our analysis focuses on recent cohorts before a growth outcome has occurred (i.e., all start-ups from 2007 to 2011). We estimate the entrepreneurial quality for each firm and then calculate the average estimated quality of firms by city and, separately, by ZIP Code. These scores can be interpreted as the expected number of growth outcomes per 1000 start-ups in the 2007–2011 cohorts.

Average quality across municipalities is shown in the first figure. Silicon Valley stands out from other regions across California: Start-ups in Menlo Park, Mountain View, Palo Alto, and Sunnyvale have 20 times the average quality of the median city and 90 times that of the lowest-ranked cities in California. Among large cities, San Francisco registers an entrepreneurial quality level nearly 8 times that of Fresno.

Entrepreneurial quality is mapped for the San Francisco Bay area at the ZIP Code level in the second figure. The quality of entrepreneurial activity is distinctively higher in the area that ranges just north of San Jose through San Francisco, with a contiguous mass of intense entrepreneurial quality from just southeast of Google (and the founding location of Fairchild) through Milbrae and Burlingame. In contrast, the Los Angeles region has a much lower level of entrepreneurial quality (fig. S2). Large economic areas can vary significantly in their quality. We investigated the statistical relation between quality and quantity (fig. S3): At best, the relation is weak and noisy. Intriguingly, across regions, entrepreneurial quality is centered around research institutions, such as universities and national laboratories. Stanford is at the heart of Silicon Valley, and University of California (UC) Berkeley; Lawrence Livermore; Caltech; University of California, Los Angeles (UCLA); and UC Irvine each host a region of distinctive entrepreneurial quality.

## Better by the Bay




**Mapping estimated entrepreneurial quality by ZIP Code.** San Francisco Bay area. Dots indicate single-address ZIP Codes. See SM.

**IMPLICATIONS.** By focusing on entrepreneurial quality, we can evaluate more clearly the role of location and institutions in firm growth. For example, our method allows us to estimate a locational entrepreneurship "premium" as the difference between realized and expected growth outcomes for a region. Between 2001 and 2006, Silicon Valley had 60% more actual growth events than predicted by our model, whereas Los Angeles registered 13% fewer than predicted.

Our method can be extended to evaluate entrepreneurial quality at arbitrary levels of geographic aggregation (e.g., a specific street in Palo Alto) (fig. S4). This facilitates fine-grained analysis of entrepreneurial dynamics (*22*), distinguishing empirically (although not causally) between locations at a high level of granularity.

Finally, beyond our characterization of Silicon Valley in the aggregate, our results highlight the role of research institutions as centers of entrepreneurial quality. Characterizing the two-way relation between entrepreneurial quality and scientific research activity is a promising agenda for future research. Although one would need to be cautious about using these estimates as a policy tool (for example, one could imagine "gaming" of various sorts), clarifying the conditions that facilitate positive growth outcomes has important implications for policy-makers and regional stakeholders.

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16. We define traded and local industries in line with the definition used in the economic cluster literature [e.g., (*15*)], and high-technology clusters are drawn from the U.S. Cluster Mapping Project [see (*15*)].
17. Many firms with the intention to grow register in the state of Delaware, where corporate law is beneficial owing to a large legal canon. Venture capitalists often prefer companies to incorporate in Delaware.
18. Our use of firm names builds on a basic assumption that entrepreneurs choose firm names conscientiously to serve as a signal to consumers, investors, and employees and that there are costs in impersonating a different type of firm.
19. An IPO or acquisition represents a significant and observable equity growth outcome from the perspective of the founders. Our ongoing research agenda also explores alternative growth outcomes in terms of employment, firm revenues, and so on.
20. Results are similar when we look at business registration and IP factors alone; see columns 1 and 2 in fig. S1.
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## ACKNOWLEDGMENTS

We thank the Jean Hammond (1986) and Michael Krasner (1974) Entrepreneurship Fund and the Edward B. Roberts (1957) Entrepreneurship Fund for financial support. We thank participants in the Massachusetts Institute of Technology (MIT) Innovation and the Digital Economy Seminar, the MIT Regional Entrepreneurship Acceleration Program, the Micro@Sloan Seminar, the Asian Innovation and Entrepreneurship Association–NBER Conference, and three anonymous referees for comments. I. Cockburn, M. Delgado, J. Gans, H. Varian, and C. Fazio provided valuable advice. We thank R. J. Andrews for excellent development of figures and visualizations, A. Carracuzzo and MIT Libraries for data support, and I. DiMambro for editorial assistance.


## SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/347/6222/606/suppl/DC1

10.1126/science.aaa0201

IMMUNOLOGY

# There goes the macrophage neighborhood

## Migrating dendritic cells disrupt lymph node macrophages and limit the immune response to secondary infection

*By* **Heather D. Hickman**

The lymph node is a highly structured organ optimized for generating adaptive immune responses. Lymph fluid carrying pathogens and their antigens from infected tissue is first distributed into a large cavity just beneath the node's surface, which is populated by a dense layer of specialized macrophages. These subcapsular sinus (SCS) macrophages filter incoming lymph, capture pathogens, and relay pathogen-derived antigen to B cells in subjacent follicles, provoking them to produce antibodies (see the figure). At the original infection site, migratory dendritic cells (DCs) are activated, acquire antigen, and deliver it to the node through the lymph, generating a secondary wave of immune cell activation. Until now, this influx of DCs has been viewed as beneficial to the host, as they activate T cells within the node's paracortex. However, on page 667 of this issue, Gaya *et al.* (*1*) demonstrate that incoming DCs can be harmful. These cells can disrupt the SCS macrophage layer and reduce the host's ability to mount a humoral (antibody) response to a secondary pathogen.

Resident antigen-presenting cells in the lymph node are commonly classified into two major subsets: DCs and macrophages. Both populations are a complex, heterogeneous mixture of cells with somewhat nebulous differences and overlapping capabilities. Even so, it is clear that different cellular subsets within each population preferentially localize to distinct regions of the lymph node where they can optimally activate discrete aspects of immune responses (*2*). For example, CD8α DCs reside in the interior of the node, are efficient exogenous antigen gatherers, and are needed for optimal T cell activation after viral infection (*3*). Several subsets of DCs are not present (in appreciable numbers) in steady-state lymph nodes, but traffic to nodes from peripheral tissue sites after infection or inflammation. Because activation, and particularly migration, take time, hours to days may elapse before immigrant DCs can influence the immune response. It is unclear how these migratory DCs precisely navigate nodal architecture to situate themselves in the node's interior; however, their arrival is essential for eliciting maximal T cell responses to many pathogens (*4*).

SCS macrophages, typically distinguished by the expression of the cell surface marker CD169 and the absence of F4/80 (found on medullary macrophages in the node), form a sessile, carpet-like layer along the floor of the SCS. After subcutaneous injection of viruses or antigen-antibody immune complexes, SCS macrophages transfer antigen on cellular processes to closely apposed B cells that lack direct access to SCS contents (*5*–*8*). This antigen-capture process both activates B cells and removes infectious material from the lymph, preventing entry into the bloodstream. Accordingly, depletion of SCS macrophages from the node before infection can result in failure to control pathogen dissemination, leading to the infection of distal organs (*6*, *9*, *10*).

> ***"The evolutionary advantage of reduced responses to ... secondary challenges is puzzling."***

Although carefully scrutinized previously with primary infection models, the behavior and function of SCS macrophages have not been systematically followed for extended periods after infection. To close this gap, Gaya *et al.* used sophisticated techniques to image skin-draining murine lymph nodes 1 week after cutaneous infection with a variety of pathogens (including *Staphylococcus*, group B *Streptococcus*, and vaccinia virus). Intriguingly, the authors observed fragmentation of the SCS macrophage layer after infection with any of the pathogens, with as much as 80% of the layer disrupted. Gaya *et al.* also assessed the ability of various additional stimuli to deplete the SCS macrophage layer. Whereas the injection of inert beads or dead

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*Science* **347** (6222), . DOI: 10.1126/science.aaa0201