sion molecule (EpCAM), which may underestimate CTC number and potentially miss a critical subpopulation (*1*, *7*). Although it has yet to be shown in spontaneously arising cancers in vivo, EMT can induce non-CSCs to enter a CSC-like state, generating CSCs de novo (*1*, *13*). However, the role of EMT in enabling metastatic dissemination is yet to be fully proven and may only operate in a fraction of cancer cells that are in close contact with adjacent reactive stroma (*1*). Present at the tumor edges, these cells may dislodge and become blood borne, i.e., CTCs. If only CTCs that undergo EMT are those with self-renewal capability and proliferative potential essential for macroscopic metastases (*13*), markers for metastatic CTCs should include EMT markers. Indeed, in many tumors, carcinoma cells exhibit a partial mesenchymal state (*1*, *9*), a phenotype absent from normal tissues (*1*). Still, it remains to be determined what fraction of CTCs lose some or all EpCAM expression and undergo (partial) EMT and whether these (or any) CTCs have increased metastatic seeding potential or heightened resistance to systemic therapy and therefore greater prognostic value. It is also unknown whether tumorigenic and nontumorigenic cells differ in their capacity to circulate in cancers that follow the cancer stem cell model. Thus, the overall relationship between CSCs and CTCs remains unclear.

That some CTCs are undetectable and not all detected CTCs have metastatic potential indicates that CTC enumeration is not a good marker for disease staging and prognosis. Instead, it is instrumental to design biomarkers based on the gene sets and genomic profile of CTC subsets that predict homing and colonization to specific distant metastatic sites or even sites of primary tumor origin. Advanced CTC analysis is being made possible by constant technical improvements in CTC detection and isolation (*7*), although there are still unresolved issues, specifically the need to standardize detection assays (*12*).

The development of single-cell analyses that can detect gene expression in individual CTCs has revealed interesting data, such as the finding of human epidermal growth factor receptor 2 (HER2)–positive CTCs in HER2-negative breast cancers (*11*). Such studies have expedited clinical trials on CTCs and indeed, the numerous ongoing trials are indicative of the vast interest in these cells. Recent genomic analysis of CTCs has detected single-nucleotide and copy-number variations generally accepted as driving forces in cancer (*14*). However, CTC genomics is still in its infancy, mainly due to a lack of technologies capable of isolating sufficient numbers of CTCs to analyze somatic mutations (*14*, *15*), and the lack of suitable material with which to compare results due to CTC heterogeneity.

The potential clinical value of CTCs is clear: Early detection and treatment of metastatic spread are key for disease outcome, and CTCs offer the ability to target metastasis in real time. Although CTCs are not yet proven to be the metastatic cells, there is no evidence that they are incapable of being so. However, a simple enumeration of CTCs without molecular characterization may lead to wrongful clinical assumptions and consequences. Elucidating CTC biology will also help standardize detection and isolation of the potentially metastatic subpopulation of CTCs. The next frontier in the CTC field is their characterization using the constantly improving single-cell "omics" techniques (*16*). This will ultimately determine the clinical value of CTCs as biomarkers and therapeutic targets.

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PHYSICS

Cold Atom Cosmology

Jörg Schmiedmayer[1] and Jürgen Berges[2]

The emergence of density fluctuations in a cloud of interacting cold atoms shows characteristic aspects of the evolution of the early universe.

At first sight, cold atoms and cosmology could not be more different; they are characterized by vastly different physical scales in energy, length, and time. On page 1213 of this issue, Hung *et al.* (*1*) report on the observation of acoustic oscillations in the time evolution of an ultracold quantum degenerate gas. This suggests that similar fundamental physics principles govern aspects of their nonequilibrium evolution.

Cosmology is time evolution. The history of the universe is imprinted on deviations from thermal equilibrium. Temperature fluctuations in the cosmic microwave background radiation are a prime example (see the figure). Analysis of these angular fluctuations has led to high-precision measurements of cosmological parameters. The increase in the fluctuation amplitude on angular scales of a degree or less is related to the phenomenon of Sakharov oscillations (*2*), where synchronously generated sound waves alternately compressed and rarefied regions of the primordial plasma. That the phases of all the acoustic oscillations were equal at some point in time during the evolution of the early universe can be understood as a result of a period of superluminal expansion or inflation (*3*).

Ultracold quantum gases provide a unique opportunity for studying nonequilibrium quantum systems. Ensembles of trapped atoms are almost perfectly isolated from the environment, and their coherent quantum evolution can be probed in detail on experimentally accessible time scales. The tunability of parameters like interaction strength, temperature, density, and dimensionality supported by powerful manipulation techniques allows the realization of many different relevant physical situations.

Hung *et al.* start from a quantum degenerate sample of cesium atoms in a highly oblate trap. The atomic sample forms an almost purely two-dimensional superfluid, tens of micrometers wide and only a few hundred

[1]Vienna Center for Quantum Science and Technology, Atominstitut, Technische Universität Wien, Stadionallee 2, 1020 Vienna, Austria. [2]Institute for Theoretical Physics, Heidelberg University, Philosophenweg 16, 69120 Heidelberg Germany. E-mail: schmiedmayer@atomchip.org

integral part of tumor staging criteria, which are currently focused on the primary tumor. Because blood collection is simple and minimally invasive, CTCs could be used as a real-time marker for disease progression and survival. CTCs also have the potential to guide therapeutic management (*7*), indicate therapy effectiveness or necessity, even in the absence of detectable metastases, and offer insights into mechanisms of drug resistance. They could be used as a surrogate endpoint marker in clinical trials (*4*), but could also become a treatment target (*7*). Despite this great potential, the use of CTCs faces many hurdles (see the figure).

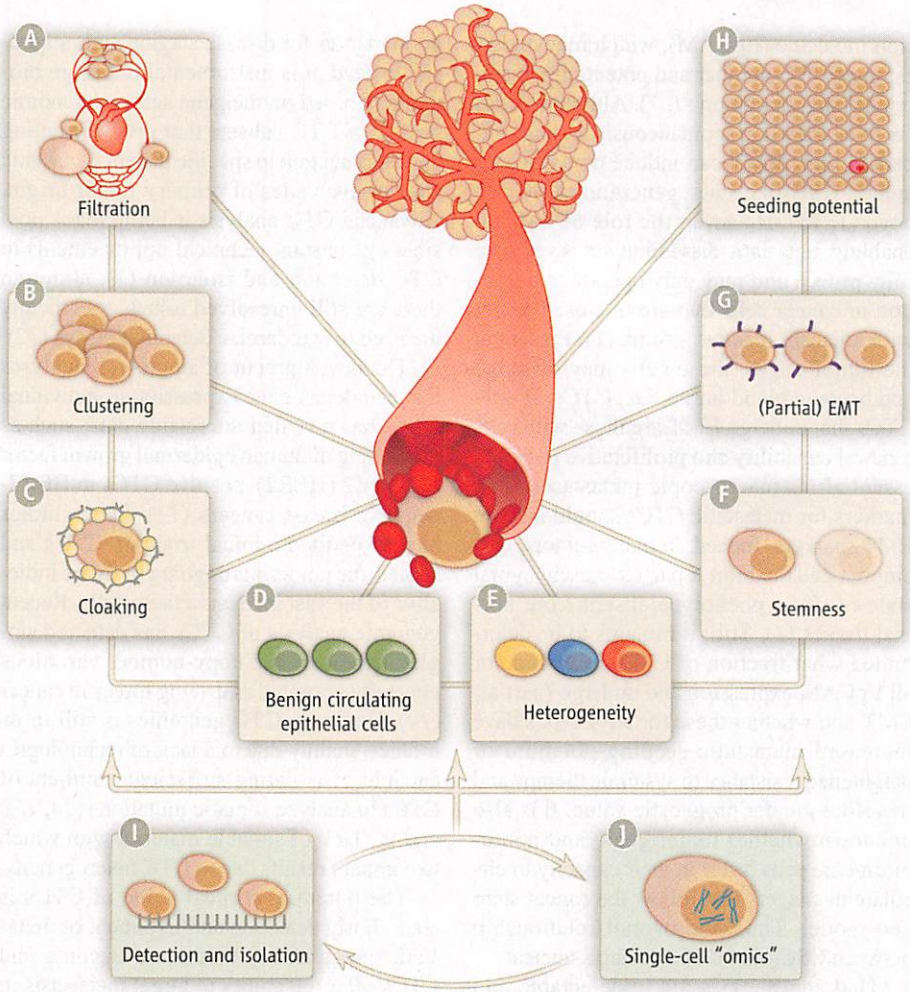
CTCs have a diameter that is three to four times as large as the bores of capillaries in distant organs, so they would be expected to become trapped there (*1*, *8*). That CTCs can be detected in the blood implies that only extremely small and/or plastic CTCs can keep circulating. And because some CTCs circulate as microclusters (*9*), these would likely also lodge in capillaries. Thus, it is unclear whether actual "circulating" tumor cells are indeed the source of metastases. Based on these points, it would be logical to assume that variations exist in the spatial and temporal distributions of CTCs within the circulation. Indeed, most solid malignancies have typical patterns of metastasis according to the localization of the primary tumor, suggesting at least partial filtration of CTCs. Thus, the site of blood collection for CTC detection may be critical. If CTCs need to be collected from various sites according to cancer type, blood sampling may not be as minimally invasive. Adding to this is the current requirement of large quantities of blood for CTC isolation and detection. Extracting blood from vessels draining the tumor may thus not be feasible and calls for the development of CTC detection devices that can handle small sample volumes. However, this poses an additional problem, because CTCs are extremely rare (*7*). For example, only 1.43% of patients with progressive breast cancer had >500 CTCs per 7.5 ml of blood (*6*). Moreover, lymphatic spread is still poorly understood (*8*), but could also be a route for tumor cell dissemination. CTCs may also be difficult to detect because they can become cloaked by platelets or by coagulation factors, thereby shielding them from the immune system. Indeed, high platelet count (thrombocytosis) is associated with poor prognosis in many cancers. Thus, a potentially metastatic subpopulation of CTCs may be currently undetectable.

Not all CTCs may be clinically relevant. Patients with various benign inflammatory colon diseases also harbored viable circulating epithelial cells detected by current CTC assays, whereas healthy subjects did not (*10*). Additionally, in a mouse model of pancreatic cancer, CTCs were found in the blood before the appearance of a primary tumor (*5*). Thus, current CTC assays are limited in distinguishing between cancer cells, noncancerous tumor components, and benign cells.

CTCs may be shed from different locations within tumors, which are heterogeneous in nature, and even from metastases. Indeed, frequently there is a clear discrepancy in gene expression between primary tumors and CTCs, as well as heterogeneity within the CTC population (*7*, *11*, *12*). It may become possible to identify the tissue of origin of CTCs by using expression profiling to detect organ-specific metastatic signatures. This would help to localize small metastatic lesions and to guide further diagnostic and therapeutic strategies.

Cancer-associated traits in some cancers have been traced to so-called cancer stem cells (CSCs). The traits that define CSCs, i.e., self-renewal, tumor-initiating, motile, invasive, and heightened resistance to apoptosis, are also instrumental for metastasis (*1*, *13*), implying that, in cancers that follow the cancer stem cell model, CTCs with high metastatic potential might be CSCs.

There is an ongoing discussion on whether tumor cells undergo epithelial-mesenchymal transition (EMT) during dissemination, resulting in a more mesenchymal or even more stem cell–like phenotype. However, current CTC detection methods mostly use the epithelial marker epithelial cell adhe-



Hurdles and solutions in CTC research. Biophysical factors that may diminish the detection of CTCs include (**A**) filtration of large CTCs in smaller capillaries, (**B**) clustering of tumor cells that lodge in capillaries, and (**C**) cloaking of CTCs by platelets or coagulation factors. Biological factors that likely complicate the detection and isolation of clinically relevant populations of CTCs that currently rely on epithelial markers include (**D**) the presence of benign circulating epithelial cells, (**E**) the large heterogeneity among CTCs, (**F**) the possible stemness of a subpopulation of CTCs, (**G**) the (partial) epithelial-mesenchymal transition (EMT) that some CTCs undergo during dissemination, and (**H**) the unclear seeding potential of detected CTCs. Future research should use technologies focused on (**I**) improving the detection and isolation of CTCs, and (**J**) single-cell "omics."

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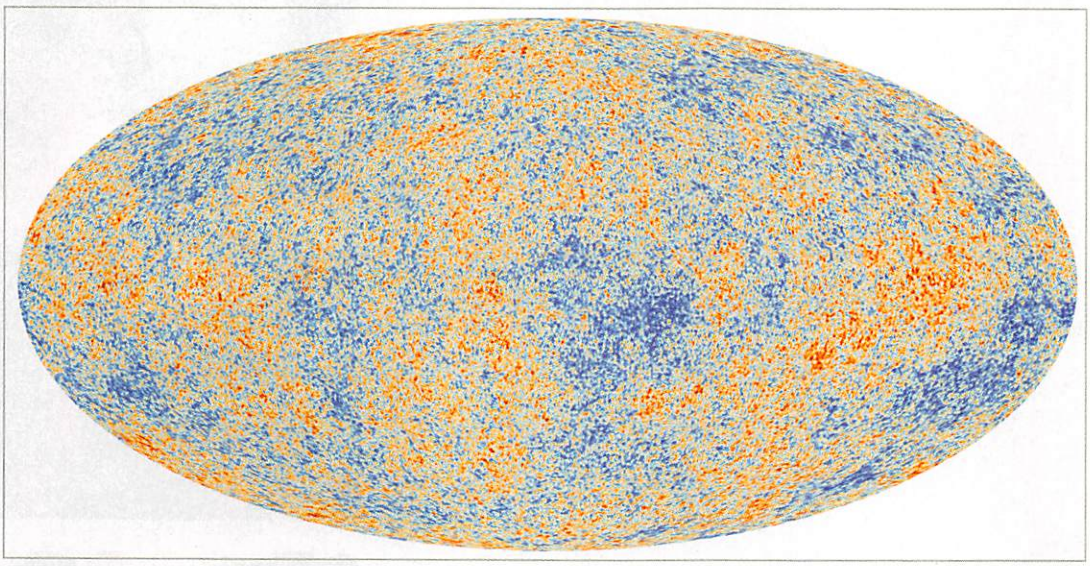

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Universal fluctuations. Temperature fluctuations in the cosmic microwave background radiation as measured by the Planck satellite. The fluctuation amplitude on small angular scales is related to the phenomenon of Sakharov oscillations.

nanometers thick at a temperature of 10 to 15 nanokelvin. Abruptly changing the atom-atom interaction strength takes the system out of equilibrium. The ensuing evolution of the nonequilibrium state shows two aspects. On long time scales (50 ms), the system adjusts its overall density profile to the new interaction energy. On shorter time scales (a few ms), density fluctuations in the cloud change dramatically. These emerging fluctuations are interpreted as Sakharov oscillations (*2*), created by the sound waves generated in the interaction quench, which then interfere as time evolves.

The speed of sound in the superfluid relates the time and length scales of interference, and Sakharov oscillations should occur only within the sound cone; outside waves do not overlap and thus do not interfere.

Such a horizon was recently observed in a different experiment studying interfering one-dimensional superfluids (*4*). Splitting a single one-dimensional superfluid into two identical systems initiated a nonequilibrium evolution of growing fluctuations in the phase, which led to decay of the initial phase coherence between the two split systems over time. The measured phase correlation function revealed that the final fluctuating state emerged locally and spread throughout the system with the speed of sound. This sound cone is in close analogy with the light cone discussed in relativistic field theories.

The appearance of similar phenomena in such vastly different settings is reminiscent of the idea of building an analog quantum simulator of the inaccessible system of study, like the early universe (*5*). Although it is far-fetched to expect the full complexity of a high-energy quantum field theory to be implemented on a degenerate quantum gas, doing so is not necessary. This relies on an important property encountered in quantum field theory: The successive inclusion of quantum corrections on different characteristic scales may be viewed as a coarse graining procedure, which finds its mathematical formulation in the theory of the renormalization group (*6*). For many macroscopic quantities, this leads to a loss of details about the underlying microscopic description. Subsequently, different systems can have similar or even the same low-energy effective theory for the quantities of interest.

This behavior is connected to the phenomenon of universality, which is well understood in thermal equilibrium. A famous example concerns scaling properties of continuous phase transitions. Near these transition points, the characteristic physics becomes scale independent and the same universal scaling exponents occur in different systems if general properties such as symmetries, dimensionality of space, or number of field components coincide. In quantum or statistical field theory, the scale invariant properties are described as renormalization group fixed points.

Similar considerations may apply also to nonequilibrium dynamics in many diverse areas of physics, ranging from the inflationary universe to complex quantum systems in condensed matter physics. For instance, inflationary models typically involve a matter field that was coherently excited out of its ground state. Its relaxation can exhibit nonequilibrium instabilities during preheating (*7*), a period of rapid entropy production leading to a prethermalized state (*8*). For the former, there are suggestions to observe similar phenomena in quantum gases (*9*). The latter predicts that thermal-like properties can emerge far from equilibrium, a phenomenon also demonstrated in an ultracold quantum gas (*10*).

An example of universality far from equilibrium, governed by nonthermal fixed points, concerns infrared scaling properties, which are predicted for inflationary models (*11*), as well as ultracold Bose gases (*12*). The associated universal phenomena leading to nonequilibrium Bose condensation (*13*), which occurs even far above the critical energy for the corresponding equilibrium transition temperature, may also be directly measured using ultracold atoms.

Finding physical implementations of gauge theories in atomic setups (*14*–*16*) may further boost our abilities of addressing problems relevant for cosmology or particle physics that are often difficult to study.

Selecting cold atom systems with suitable Hamiltonians offers the prospect to learn at least qualitatively about otherwise inaccessible phenomena. For universal aspects, this gains more predictive power and, despite the vast differences in characteristic scales, we may indeed learn from table-top experiments with cold atoms quantitative aspects about the dynamics during the very early stages of our universe.

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